Examining the neural basis of decisionmaking using social stimuli, dopamine and oxytocin in schizophrenia

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Examining the neural basis of decision-making using social stimuli, dopamine and oxytocin in schizophrenia

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ABSTRACT

Background: Schizophrenia is a devastating disorder, treated with antipsychotics acting via dopaminergic D_2 blockade, and significant comorbidity impacting through social dysfunction. The neural mechanisms underlying the processing of socially salient material and the dopaminergic networks posited to be central to this social decision making remain unclear. These mechanisms are explored in this thesis.

Methods: fMRI was performed on 20 healthy controls (HC) treated with single dose of a dopamine agonist, ropinirole (0.25mg); dopamine antagonist, amisulpride (400mg), and placebo. fMRI was also performed in 42 patients with schizophrenia (SZ); and a subsample of 20 patients after treatment with oxytocin (40IU) or placebo nasal spray. Participants performed a decision-making task incorporating stochastically rewarded faces of varied social valence during the fMRI.

Results: The normal bias towards selecting a happy face was attenuated by all pharmacological agents (ropinirole, amisulpride and oxytocin). In HC, attenuation of bias after ropinirole administration was accompanied by an increase in neural activity within the dorsal anterior cingulate and dorsomedial prefrontal cortex and attenuation in the amygdala. In SZ, attenuation of bias after oxytocin administration was accompanied by attenuation of neural activity in the temporoparietal junction and amygdala. When looking between groups, SZ showed attenuated neural activity in the thalamus, cerebellum and medial prefrontal cortex (mPFC). HC on amisulpride showed similar attenuation in the cerebellum to SZ.

Discussion: Modulation of processing of socially salient stimuli was evident during the perturbation of the dopaminergic system, impacting both behaviour and neural

processing. The key regions demonstrating change between HC and SZ were the thalamus, cerebellum and mPFC; supporting a deficit in the coordination and integration of decision-making following the cognitive dysmetria model. Oxytocin demonstrated prosocial effects in SZ, through modulation of amygdala activation; and showed some overlap with dopaminergic responsive regions, lending support to a possible action via the dopaminergic system.

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CHAPTER 1 - INTRODUCTION

1.1 SCHIZOPHRENIA

Schizophrenia is a very debilitating illness which has a lifetime prevalence between 0.3% to 0.66% (McGrath et al., 2008). It remains one of the costliest disorders in terms of both social and economic costs (Knapp et al., 2004). Schizophrenia is characterised by the presence of positive and negative symptoms as well as altered pathophysiological processes, such as aberrant neurochemical pathways. Positive symptoms are the core symptoms presented in schizophrenia. These positive symptoms are symptoms that most people do not normally experience but are manifested in schizophrenia. They include delusions (i.e. fixed false beliefs that are firmly held despite being bizarre or implausible, for example the belief that one's thoughts are being broadcast; or the feeling of being controlled by external forces) as well as hallucinations (e.g. the perception of voices that no one else can hear which may comment on one's actions or give their own commands). Negative symptoms, on the other hand, refer to experiences that are absent in individuals with schizophrenia as compared to the healthy population. These include stunted emotional responses, the inability to experience pleasure (i.e. anhedonia), a decreased desire to seek meaningful relationships with others, decreased speech, and a general lack of motivation. Additionally, although not an official diagnostic criteria, patients with schizophrenia also exhibit impairments in almost all cognitive domains (Carroll, 2000; Kraus and Keefe, 2007), including decision-making tasks (Heerey et al., 2008; Hutton et al., 2002; Larquet et al., 2010) and tasks that require social cognition (Couture et al., 2006; Fett et al., 2011; Lee et al., 2004). Generalised cognitive impairment, indexed by IQ, precedes the onset of psychosis and is detectable as far back as infancy (Khandaker

et al., 2012). In addition, the severity of impairment is linearly related to the risk of developing psychosis and predicts functional outcome following illness onset (Khandaker et al., 2012; Leeson et al., 2009). Most importantly, cognitive impairments have been closely linked to one of the most debilitating issues in schizophrenia: the impairment in everyday life functioning (Green, 1996; Green et al., 2000; Kraus and Keefe, 2007). Further to cognitive deficits, deficits in social functioning are a defining characteristic of schizophrenia; and a marked impairment in social or occupational competency is a requirement for diagnosis (DSM-IV, 2000). Social dysfunction is evident in the premorbid phase of the illness (Davidson et al., 1999), and in first-degree relatives (Glatt et al., 2006), confirming its status as a trait marker for the disorder. Furthermore, impaired social cognition predicts functional outcome in schizophrenia, impacts affect quality of life (Couture et al., 2006; Penn et al., 1997) and has been more strongly associated with community functioning than other cognitive variables (Fett et al., 2011). Social and cognitive impairments significantly impact the way in which patients with schizophrenia process beliefs about the (social) world around them and social cognition deficiencies in schizophrenia impair the formation and maintenance of social relationships which may contribute to the instantiation and perseverance of some symptoms observed in schizophrenia. Cognitive and social impairment are thus core features of schizophrenia that significantly impact on the course of illness; warranting a more detailed understanding of its generalised nature and neurobiological basis (Roiser et al., 2013).

1.1.1 AETIOLOGY OF SCHIZOPHRENIA

Although schizophrenia has been the subject of much research since its recognition as a disorder over 100 years ago (Bleuler, 1908), its exact aetiology is still unclear. A

number of theories have been posited to explain how the symptoms of schizophrenia arise. One of these theories is the glutamate hypothesis, or the idea that aberrant levels of glutamate due to aberrant functioning of N-methyl-D-aspartate (NMDA) receptors (Coyle, 2006; Stephan et al., 2009; Stone et al., 2007). Support has been garnered for this theory by the observation that NMDA receptor antagonists, such as ketamine, have the ability to induce both the positive and negative symptoms associated with schizophrenia as well as research showing NMDA receptor gene expression abnormalities in schizophrenia (Moghaddam and Javitt, 2012). A follow up hypothesis to abnormalities induced by aberrant NMDA functioning is the concept of dysconnectivity or the idea that aberrant NMDA receptor mediated synaptic plasticity leads to abnormal functional connectivity between different areas of the brain due to abnormal regulation of NMDA receptors by neuromodulatory transmitters such as dopamine, serotonin or acetylcholine (Pettersson-Yeo et al., 2011; Stephan et al., 2006; Stephan et al., 2009). Andreasen and colleagues specified that they believe many of these symptoms arise through specific dysconnectivity between the mPFC, thalamus and cerebellum, a theory which they refer to collectively as cognitive dysmetria (Andreasen et al., 1999; Andreasen et al., 1996; Andreasen et al., 1998). However, there are two main hypotheses that have been developed over the years which are proposed to explain the genesis and neurological underpinnings of schizophrenia: the neurodevelopmental hypothesis and the dopamine hypothesis.

1.1.1.1 NEURODEVELOPMENTAL HYPOTHESIS OF SCHIZOPHRENIA

The neurodevelopmental hypothesis posits that schizophrenia arises due to a disruption in brain development during earlier stages of life which later leads to the emergence of symptoms observed in schizophrenia (McGrath et al., 2003; Owen et al., 2011). This theory has been supported by studies demonstrating that early life

exposure to risk factors such as birth complications, influenza epidemics and stress can significantly increase the risk of developing schizophrenia; as well as longitudinal studies showing that those who go on to develop schizophrenia tend to have poorer motor skills and language difficulties (Cotter and Pariante, 2002; McGrath et al., 2003). Furthermore, patients with schizophrenia tend to show neuropathological differences in the brain such as ventricular enlargement and decreased cortical and hippocampal volume, which are common across all subtypes including first-episode, medicated and unmedicated patients with schizophrenia (Harrison, 1999). The neurodevelopmental theory accounts for a gradual development of schizophrenia over time due to disruptions in early brain development, yet it does not fully explain what neural processes cause the symptoms of schizophrenia due to these disruptions. Many observations have led to the theory that an aberrant dopaminergic system may be responsible for some of the symptoms observed in schizophrenia.

1.1.1.2 DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

1.1.1.2.1 DOPAMINE

The neurotransmitter dopamine has long been viewed as a key player in reward related processes to have an effect on motivation, incentive salience, conditioned reinforcement, memory consolidation as well as addiction (Wise, 2004). It has been implicated in a wide range of neurological processes including reward prediction, reinforcement learning, executive function; motor control and working memory. It has been implicated in a range of disorders next to schizophrenia, for example substance abuse or Parkinson's disease. It is one of the most studied neurochemicals in neuroscience and, due to its role in learning mechanisms, has recently become heavily modelled in the field computational neuroscience. It is believed that dopamine models

prediction errors (i.e. the difference between the predicted value and the actual value).

When presented with a reward, dopamine will spike in the brain (Glimcher, 2011). If an action is paired with this reward, it is possible to create a learned effect, due to the association between the action and the reward. This association is known as conditional learning. Repeating this association over time leads to a "stamping-in" of this association referred to as reinforcement learning (Wise, 2004). By aiding in learning between an action and a reward, dopamine plays a role in memory consolidation and encoding. The desire to keep repeating this action for a reward is how dopamine is associated with motivation. For example, when given dopamine antagonists, rats will show a decrease in their initiation and perseverance of this reward seeking behaviour (Bardgett et al., 2009; Wise, 2004). Furthermore, rats treated with dopamine antagonists will show deficits in learning to associate actions such as lever pressing with rewards (Parkinson et al., 2002; Wise, 2004).

1.1.1.2.1.1 DOPAMINE PROPERTIES

Dopamine is comprised of two different families of G-protein coupled dopamine receptors, each with different pharmacological properties mainly derived from their interaction with adenyl cyclase (AC), D_1 family receptors and D_2 family receptors. D_1 family receptors are comprised of D_1 and D_5 while D_2 family receptors are comprised of D_2, D_3 and D_4 receptors. From this point onward, I will refer only to these families of receptors unless otherwise specified. D_1 receptors are coupled with the G_s protein and act by stimulating AC thus increasing intracellular concentrations of cAMP (Williams and Castner, 2006). D_2 receptors act in the opposite direction; they are coupled with the G_i protein and directly inhibit the formation of the AC enzyme which, in turn,

inhibits the formation of cAMP (Williams and Castner, 2006). Both families of receptors act along four major pathways in the brain, the mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular dopaminergic pathways. Of these, the mesolimbic and mesocortical are believed to be the most influential in the instantiation and perseverance of schizophrenia. The mesolimbic pathway projects from the ventral tegmental area (VTA) to areas of the limbic system and plays a role in motivation and pleasurable sensations (Arias-Carrion et al., 2010).

Hyperactivation of the mesolimbic pathway is believed to be responsible for the formation of delusions and hallucinations in schizophrenia possibly through the attribution of aberrant salience, where seemingly innocuous events are imbued with increased salience due to a hyperdopaminergic state (Kapur, 2003). The mesocortical pathway, which projects from the VTA to regions of the prefrontal cortex (PFC), is believed to play a role in cognition and affective symptoms. Hypoactivation of this pathway is thought to lead to cognitive deficits via the dorsolateral PFC (dlPFC) and affective or negative symptoms observed in schizophrenia via the ventromedial PFC (vmPFC). The nigrostriatal pathway projects from the substantia nigra (SN) to the basal ganglia or striatum and is part of the extrapyramidal nervous system which controls motor function and movement. This pathway is believed to be normal in schizophrenia although antipsychotics sometimes cause hypoactivation of this pathway leading to extrapyramidal side-effects such as akinesia and akathisia.

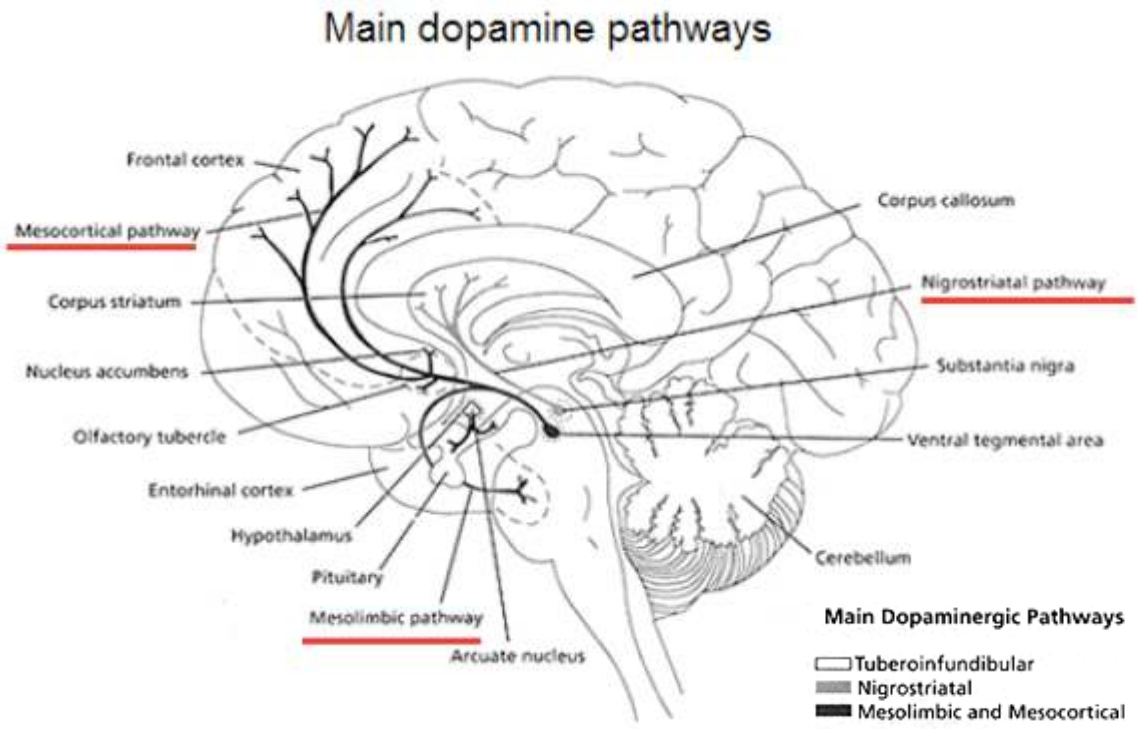

FIGURE 1.1 - Figure showing the main dopaminergic pathways involved in the actions of antipsychotic drugs. Taken from: (Bethopedia, 2012)

The original dopamine hypothesis posited that schizophrenia arises due to hyperactive dopaminergic systems in schizophrenia (van Rossum, 1966). A variety of evidence has accumulated in support for this hyperactive dopaminergic system in schizophrenia. However, a hyperactive system only accounts for the positive symptoms observed with schizophrenia, whereby increased dopamine leads to psychosis. A revised theory posited that hyperactivity in D_2, mainly within the mesolimbic pathway, was responsible for the positive symptoms while hypoactive D_1 receptors, mainly those in the frontal brain areas, were responsible for the negative and cognitive deficits also observed in schizophrenia. Although it is currently unable to explain all of the symptoms of schizophrenia, the dopamine hypothesis does offer a direct line of evidence between many of the symptoms of schizophrenia and their cessation with treatment. Initial support came from studies showing that neuroleptic drugs interfered with brain dopamine function (Baumeister and Francis, 2002; Carlsson and Lindqvist,

1963). Initial links of neuroleptics to dopamine showed that nonreserpine neuroleptics were dopamine antagonists as they were able to activate dopamine receptors and block stimulus induced movement as well as studies which implicated dopamine in neuroleptic-induced extrapyramidal motor symptoms (Carlsson and Lindqvist, 1963) (for a review see (Baumeister and Francis, 2002)). Research also found that high doses of psychostimulants, mainly amphetamine, induced paranoid psychosis in those that had not been previously diagnosed with psychosis (Angrist and Gershon, 1970; Griffith, 1968). However, these early studies only reported on the positive symptoms which they observed with only anecdotal references to negative symptoms as these were not classically recognised as a class of symptoms of schizophrenia until (Crow, 1980). In further accordance with these observations, it was demonstrated that, in patients with schizophrenia, low doses of psychostimulants that did not induce psychosis in healthy subjects could exacerbate or induce psychosis in patients with schizophrenia (Lieberman et al., 1987; Ujike, 2002). However, this response also appears to be state dependent and does not occur when a patient is in remission. One of the most convincing pieces of evidence came with the observation that the clinical efficacy of an antipsychotic drug is directly proportional to its affinity for dopamine receptors (Creese et al., 1976; Ginovart and Kapur, 2012; Seeman and Lee, 1975). Furthermore, to this day, all antipsychotics used clinically bind to D_2 receptors. However, none of these studies adequately explained how dopamine affected negative and cognitive symptoms. Additionally, post-mortem studies did not reveal consistent elevation in dopamine throughout the brain nor could these studies exclude the effects of prior antipsychotic use (Bacopoulos et al., 1979; Bird et al., 1977; Crow et al., 1979; Reynolds, 1983; Toru et al., 1982). A revised hypothesis (Davis et al., 1991) posited a more regional specificity of dopamine in schizophrenia. Evidence from further studies

showed reduced cerebral blood flow to the frontal cortex (Davis et al., 1991; Weinberger et al., 1986) and that hypofrontality correlated with low dopamine metabolite levels in the cerebrospinal fluid (CSF) (Doran et al., 1987). Doran and colleagues proposed that schizophrenia was caused by hypodopaminergia in the prefrontal cortex as well as by hyperdopaminergia in the subcortical regions. They also hypothesised that this hypodopaminergia was responsible for the negative symptoms observed in schizophrenia. Further to this, a "final common pathway" was proposed by Howes and Kapur (2009), stating that the dopamine dysregulation is caused by multiple direct and indirect environmental and genetic factors and that this dysregulation is caused at the presynaptic level. Furthermore, they hypothesised that dopamine dysregulation results in the faulty appraisal of stimuli resulting in the attribution of aberrant salience such that seemingly innocuous stimuli are accorded much higher salience (Kapur, 2003). This is important in schizophrenia as it shows how patients with schizophrenia may place increased importance on stimuli that would not hold value for others thus leading to the formation of delusions.

In line with these theories around dopaminergic involvement in schizophrenia, all current antipsychotic drugs which are prescribed act as D_2 antagonists. While these drugs are effective in the treatment of positive symptoms of schizophrenia, they still have limited efficacy on the negative symptoms and social functioning deficits observed in schizophrenia (Gray and Roth, 2007; Penn et al., 2009; Sergi et al., 2007). The need to find newer drugs which can alleviate these distressful symptoms is paramount for the progression of treatment in schizophrenia.

4.1.1.1.1.1 OTHER NEUROCHEMICALS

Two other neurochemicals which also may contribute to the pathology of schizophrenia are serotonin (5-hydroxytryptamine, 5-HT) and glutamate. Glutamate is the most prevalent neurotransmitter in the human brain, representing about half of the neurotransmitters in the brain and can be found throughout the brain. Serotonin is primarily produced in the raphe nuclei which are located in the brain stem. These nuclei then project to regions of the gastrointestinal tract as well as the CNS. Axons from the raphe nuclei project to the spinal cord and cerebellum as well as to the thalamus, nucleus accumbens, hypothalamus, hippocampus, amygdala, cingulate cortex, including the cingulum and the neocortex (Berger et al., 2009). Both neurochemicals are fairly ubiquitous in their projections within the brain, extending throughout most regions of the brain.

1.2 OXYTOCIN

One neurochemical that has been posited to have a beneficial effect on the social functioning deficits observed in schizophrenia is oxytocin. The role of oxytocin in social behaviour has been well established. It plays an important role in parturition, milk ejection, sexual function, attachment and parenting behaviour (Insel and Young, 2001a; Meyer-Lindenberg et al., 2011). In experimental studies, oxytocin has been linked to the facilitation of social behaviours such as trust (Baumgartner et al., 2008; Kosfeld et al., 2005) and parental bonding (Galbally et al., 2011). It has also been shown to increase the ability to identify emotions, increase empathy toward others, and to attenuate aversion to angry faces (Bartz et al., 2011; Evans et al., 2010; McCall and Singer, 2012). Additionally, it also helps regulate intergroup conflict by enhancing intergroup trust and cooperation while at the same time increasing defensive

aggression toward out groups (De Dreu, 2012; De Dreu et al., 2011). Furthermore, its role in facilitating social interactions by ameliorating social bias and response to emotional faces has led it to be considered as a possible drug to use in disorders with severe social deficits such as autism and schizophrenia (Evans et al., 2010; Guastella et al., 2013).

1.2.1 OXYTOCIN PROPERTIES

Oxytocin is synthesised in the hypothalamic paraventricular parvocellular neurons (PVN) and the supraoptic nuclei (SON) and is then secreted by the posterior pituitary. Neurons from the PVN project to various areas in the limbic system (hippocampus, amygdala, striatum, hypothalamus and nucleus accumbens), brain areas which are also heavily involved in social cognitive processing (Gimpl and Fahrenholz, 2001).

4.1.2 OXYTOCIN AND SCHIZOPHRENIA SYMPTOMATOLOGY

When directly measuring oxytocin levels in the CSF and plasma, no differences have been found between healthy controls and patients with schizophrenia (Beckmann et al., 1985; Gattaz et al., 1985; Glovinsky et al., 1994; Sasayama et al., 2012b; Walss-Bass et al., 2013). However, numerous studies looking at oxytocin levels within both the CSF and plasma have found that in both healthy controls and patients with schizophrenia measures associated with the symptomatology of schizophrenia (e.g. positive and negative symptom scores, and delusions) and prosociality correlated with oxytocin levels. Within the CSF, oxytocin levels in patients with schizophrenia correlated with negative symptoms (Sasayama et al., 2012b). In the plasma, higher levels of oxytocin were associated with greater prosocial behaviours (Rubin et al., 2010) and predicted the ability of patients with schizophrenia to identify facial expressions correctly (Goldman et al., 2008). Additionally, plasma oxytocin levels were found to correlate

with negative, but not positive symptoms, depression, anxiety and neuropsychological functioning (Keri et al., 2009). Furthermore, in both patients with schizophrenia and healthy controls, plasma oxytocin levels were found to correlate with delusional thought content, where lower oxytocin levels predicted more delusional thoughts (Walss-Bass et al., 2013). Together, these findings show that oxytocin levels within the body offer putative correlations to symptomatology measures which affect sociality in both healthy controls and patients with schizophrenia.

1.2.2 OXYTOCIN AS A THERAPY

Although dopaminergic medications are currently able to treat the positive symptoms of schizophrenia quite well, the social deficits of schizophrenia currently remain untreated. Oxytocin provides a putative mechanism for treating these social deficits. In patient groups, preliminary work has proved encouraging in schizophrenia, as well as in other disorders that have been associated with profound social dysfunctions such as autism and social anxiety disorders. In subjects diagnosed with autism, oxytocin has been shown to improve comprehension of affect information in speech (Hollander et al., 2007) and promote emotion recognition (Guastella et al., 2010); in social anxiety disorder, oxytocin alleviates negative self-perception following exposure therapy (Guastella et al., 2009). Clinical trials of oxytocin in patients with schizophrenia offer preliminary support for its efficacy. All studies but one which looked at the effect of oxytocin administration on the outcome of the positive and negative symptom scale (PANSS), have found a significant reduction in various symptom scores after patients with schizophrenia had taken oxytocin compared to a placebo after two to eight weeks of oxytocin administration (Feifel et al., 2010a; Gibson et al., 2014; Modabbernia et al., 2013; Pedersen et al., 2011a). A meta-analysis of these studies (with the exception of

(Gibson et al., 2014)) found a modest effect size of treatment across positive, negative and general symptoms (Gumley et al., 2014). However, only two of these studies addressed the effects of repeated oxytocin administration on social cognition. One study showed an improvement in Theory of Mind tasks patients with schizophrenia given oxytocin versus placebo (Pedersen et al., 2011a), while another suggested improvements in verbal memory function post oxytocin treatment (Feifel et al., 2012b). Overall, these studies suggest that oxytocin administration may offer potential benefits for patients with schizophrenia across symptom scores and social domains but further research needs to be done to highlight the specificity for these effects and what factors may contribute to how oxytocin differentially affects patients with schizophrenia and who may benefit the most from treatment.

While these studies suggest that, over time, oxytocin may have an effect on symptomatology in schizophrenia; other studies have also explored the acute effects of oxytocin administration on general social cognition. Given that studies in healthy controls have shown changes in behavioural and neural activity after oxytocin administration (Wigton et al.), ranging from tasks looking at trust (Baumgartner et al., 2008) to exploring ingroup outgroup dynamics (De Dreu, 2012; De Dreu et al., 2011), a few studies in patients with schizophrenia have been conducted to see if these findings could be replicated to improve social cognition in patients. These studies have shown that oxytocin administration is capable of increasing the ability of patients with schizophrenia to accurately identify emotions (Averbeck et al., 2012) as well as increasing the degree of empathy that patients with schizophrenia show toward an in-group (Abu-Akel et al., 2014) compared to a placebo. Acute oxytocin administration has also been shown to significantly improve “controlled social cognition,” or how

indirectly expressed social stimuli such as emotions, thoughts, intentions and complex deliberations are understood over longer periods of time, similar to theory of mind tasks, but not "automatic social cognition," or how social cues from the voice, face and body are interpreted, for example, explicit emotion recognition (Woolley et al., 2014). Together, these studies suggest that, even with an acute dose, oxytocin administration offers potential benefit to patients with schizophrenia in interpreting social cue and in increasing more complex social processing such as empathy and theory of mind.

Although oxytocin seems to have promising potential for enhancing social cognition, fundamental questions regarding the mechanism underpinning the oxytocin effects on social processing need to be addressed to establish its therapeutic potential in clinical practice. In healthy controls, oxytocin administration appears to influence behaviour through an attenuation of neural activity in social regions such as the amygdala, at least in male participants. This attenuation has resulted in the facilitation of prosocial behaviours such as increased trust (Baumgartner et al., 2008) and emotion recognition (Gamer et al., 2010a) in healthy controls but has yet to be explored in patients with schizophrenia.

1.2.3 DOPAMINE AND OXYTOCIN

Recent evidence has emerged showing a possible relationship between oxytocin and dopamine. There is research linking midbrain and mesolimbic dopamine with the effects of oxytocin on the processing of social stimuli**.** A few studies have shown that dopamine is involved in mediating some of the same maternal (Shahrokh et al., 2010) and pair bonding (Wang and Aragona, 2004) behaviours that are exhibited under the influence of oxytocin. In rabbits, some of the same disturbances seen in the hippocampal EEG and behaviour under oxytocin are also observed under dopamine

agonists (Maurelli et al., 1988). In humans, oxytocin has been implicated in helping to mediate addiction and withdrawal in the mesolimbic dopaminergic pathways (Baskerville and Douglas, 2010b). Furthermore, differences in peripheral and central levels of oxytocin have been found in patients with disorders with potential dopamine abnormalities such as autism (Al-Ayadhi, 2005; Anderson et al., 2008; Hamilton et al., 2013; Previc, 2007), schizophrenia (Howes et al., 2012; Howes and Kapur, 2009; Laruelle and Abi-Dargham, 1999; Sasayama et al., 2012a) and social anxiety disorder (Bell et al., 2013; Fink et al., 2009; Hoge et al., 2008; Schneier et al., 2009). Preclinical studies have shown that dopaminergic fibres may regulate oxytocin release (Lindvall et al., 1984; Melis and Argiolas, 2011) and that the receptor binding sites and neuronal fibres of both of these neurochemicals reside in the same regions of the CNS and are often next to each other (Baskerville and Douglas, 2010b; Schwartz et al., 1994; Smeltzer et al., 2006a). Further evidence suggests that, at least in the ventral and dorsal striatum, D_2 dopamine receptors and oxytocin are heteromers with facilitatory receptor to receptor interactions (Romero-Fernandez et al., 2012). Evidence from these studies leads to the proposal that dopamine and oxytocin may work together to regulate behavioural responses to social stimuli, such that dopamine affects the assignment of emotional salience (Laviolette, 2007) while oxytocin modulates amygdala tone (Rosenfeld et al., 2011).

1.3 MODELLING DECISION-MAKING AND DOPAMINE

Decision-making is comprised of a series of cognitive processes with the intention of selecting the best action from a competing set of beliefs or possibilities. The formation of beliefs and their subsequent integration into views of the world and actions is what drives decision-making. This is important because it determines how actions are

executed and, in turn, how the results of those actions are interpreted. In schizophrenia, this process has been shown to be impaired during the formation of preference, execution and outcome evaluation (Ernst and Paulus, 2005b).

In a Bayesian sense, the actions of others can be interpreted on the basis of probabilistic inference by which a new model of the world is derived from old evidence (priors) and new experiences or evidence (likelihoods). These types of models base their outcomes on how well one is able to integrate both old and new evidence to generate a belief about the world and what level of pertinence is allocated to each piece of evidence. A common way to assess neural correlates from these types of tasks has been to use prediction errors, conventionally conceptualized in terms of the difference between predicted and actual reward outcome, to determine the effects on cognition (Montague and Berns, 2002; Pessiglione et al., 2006). These signals predict activity in structures with strong dopaminergic connections such as the ventral striatum (O'Doherty et al., 2003; Pessiglione et al., 2006; Wittmann et al., 2008), or, more generally, the caudate and putamen (Gradin et al., 2011; Sanfey, 2007; Waltz et al., 2011), which makes this modelling extremely useful to assess the influence of dopamine on reward processing during decision-making. Furthermore, it is thought that functional or structural damage to the neural mechanisms controlling these areas may be a fundamental pathophysiology leading to disorders such as schizophrenia (Brune, 2005a, b) and that this pathophysiology may be brought about due to a dysregulation of dopamine from its integral role in reward learning (Berridge and Robinson, 1998; Kapur et al., 2005). In this regard, deficits have been consistently observed over all subtypes of the illness, including in unmedicated patients (Andreasen et al., 2008) and remitted patients (Marjoram et al., 2006). With this in mind, using probabilistic models, it has been possible to assess computational aberrance in

dopaminergic systems in schizophrenia (Gradin et al., 2011; Morris et al., 2012; Murray et al., 2008; Waltz et al., 2011). However, this approach still insufficiently explains the more complex processes underlying decision-making, its neural correlates, and related dysfunction in schizophrenia.

1.4 USE OF DOPAMINE AGONISTS AND ANTAGONISTS TO PROBE BRAIN FUNCTION

The use of dopamine agonists and antagonists to probe neural function is not in itself a new idea. Previous studies that have used both drugs were mainly done in rats to show that dopaminergic manipulation has a significant effect on impulsive decision-making, Specifically, increases in dopamine have been shown to increase impulsive decision-making (e.g. rats choose a lower immediate reward more often than waiting for a larger delayed reward (van Gaalen et al., 2006)); and dopamine antagonists have been found to decrease the rats' motivation for pursuing any reward (Franklin and McCoy, 1979) (for a review see (Wise, 2004)).

Only a handful of studies have looked at the effect of dopamine agonists and antagonists in human healthy participants using neuroimaging. Most studies have used a decision-making paradigm in which subjects are asked to determine through trial and error which of two probabilistically rewarded stimuli has the highest probability of being rewarded in each trial. These studies have shown how dopaminergic manipulation allows for the modulation of both behaviour and neural activity in humans. In Pessiglione et al. (2006), subjects had a higher tendency towards picking the more rewarding option than after receiving a dopamine agonist (L-DOPA) compared to a dopamine antagonist (haloperidol). This study also showed that dopaminergic drugs modulate reward prediction error signals in the striatum and that

the magnitude of this modulation could be modelled by how the drugs affected behavioural choices, such that L-DOPA increased neural activity correlating with RPE in the striatum and increased the tendency to choose the more highly rewarded stimuli while haloperidol had the opposite effect (Pessiglione et al., 2006). However, another study by Bernacer et al. (2013), showed that dopamine agonists actually may disrupt decision-making. The authors used methamphetamines as a dopamine agonist, together with methamphetamines combined with a dopamine antagonist (amisulpride) and a placebo condition. They found that methamphetamine attenuated the amount of activity in correlating with the encoding of incentive values, or RPE, in the limbic striatum, as well as attenuating the amount of neural activity in the ventromedial prefrontal cortex (vmPFC) correlating with incentive value. Thus methamphetamines were found to disrupt neural activity associated with learning signals in the brain. Pretreatment with amisulpride did not alter the effects of methamphetamines in the striatum or in the vmPFC suggesting that, in this study, effects may have also been driven by something other than dopamine D_2 receptors such as norepinerphrine or dopamine D_1 receptors. Another study that looked at how dopamine antagonists modify value based decision-making, found that the dopamine antagonist (amisulpride) improved the ability of participants to learn better reward contingencies between two highly rewarding stimuli, but that it had no effect on learning rates when stimuli were poorly rewarded. Furthermore, during this task reward prediction error signals in the striatum were enhanced by amisulpride (Jocham et al., 2011) suggesting that some dopamine antagonists are actually able to enhance behavioural performance and neural activity.

During non-classical decision-making tasks, the dopamine agonist (L-DOPA), an antagonist (haloperidol) and a placebo modulated behavioural and neural effects of sensory decision-making (involving discriminating the speed or rhythm of a "tickling sensation" on their finger occurred) (Pleger et al., 2009). In this study, L-DOPA enhanced neural activity within the primary sensory cortex and haloperidol attenuated neural activity within this area. Interestingly, this study did not find a significant drug effect within the striatum, but they did find a modulatory effect of reward value within the primary sensory cortex. The second study also used L-DOPA, haloperidol and a placebo but in this study, subjects were presented with subliminal sexual images that required no decision-making. They found that neural activity within the dorsal anterior cingulate (dACC) and nucleus accumbens was enhanced by L-DOPA and attenuated by haloperidol, suggesting that these regions also respond to subconscious sexual reward which is modulated by dopamine (Oei et al., 2012). It is important to note that drug pharmacodynamics can vary with dose, though this differs between compounds and individuals, the specifics of how each drug interacts with different neural systems are commonly not well circumscribed. Collectively, these studies show that dopaminergic manipulation produces changes in neural activity - where dopamine agonists (or at least L-DOPA) typically increase neural activity in reward related regions with high dopamine receptor densities, while dopamine antagonists (at least haloperidol) typically attenuate neural activity within these regions but that these findings are discordant when using other dopaminergic compounds.

1.5 AIMS OF THIS THESIS

In this thesis, I aim to use functional magnetic resonance imaging (fMRI) to explore neural activity after the administration of pharmacological probes during an

associative learning decision-making task which incorporates emotionally valenced and neutral faces as social variables. I propose to explore how dopamine, oxytocin and the processing of socially salient affective stimuli influences decision-making in patients with schizophrenia through assessing neural activity compared to healthy controls in the core regions associated with decision-making and social processing.

I will assess changes in hemodynamic activity in the brain using functional magnetic resonance imaging (fMRI) after the administration of oxytocin and dopamine upon the networks and regions that contribute to associative learning and decision-making in healthy controls and patients with schizophrenia. The same task is used across all the studies in this thesis to allow for a more direct comparison of drug and group effects.

The purpose of the first part of this study was to explore the effects of dopaminergic manipulation in healthy controls and compare these perturbations to patients with schizophrenia. The rationale behind this was to observe similarities and differences between dopaminergic activity in patients and manipulated levels in controls. Given that dopamine appears to play a large role in the substantiation of psychosis, mainly in the realm of positive symptomatology, dopaminergic binding within the brain was manipulated in healthy controls using a dopamine agonist (ropinirole), antagonist (amisulpride) and placebo. The idea behind this manipulation was to give a clearer picture of how the changes from dopamine perturbation could relate to changes observed in patients with schizophrenia during decision-making with an element of implicit social processing. In the second part of the study, the aim of the study was to explore the effects of oxytocin administration using the same task in patients with schizophrenia. Given oxytocin's recent popularity as potential treatment alternative for the deficits in social cognition observed in schizophrenia, as well as its putative links

with the dopaminergic system; this second study looked to see how neural activity would be affected by oxytocin administration in schizophrenia and see if there were any commonalities with changes in neural activity after dopaminergic perturbation.

Part 1: The effect of dopamine on decision-making and its relation to schizophrenia

Chapter 3 will explore how dopaminergic perturbations using the dopamine agonist, ropinirole, and the dopamine antagonist, amisulpride, affects neural activity and performance compared to a placebo when deciding which of two faces has a higher probability of being rewarded out of two emotionally valenced faces (i.e. an angry or happy face) or two neutral faces of different identites. **Chapter 4** will explore the task in patients with schizophrenia compared with data from healthy controls**.**

Part 2: The effect of oxytocin on decision-making in schizophrenia

As the main focus of the first two chapters is in regard to dopamine, **Chapter 5** will give an overview of oxytocin and its use in neuroimaging studies as well as providing a brief overview of how oxytocin may be related to the dopaminergic system and how it may benefit disorders with social impairment such as schizophrenia.

Chapter 6 will use the same task as in Chapters 3 and 4 but will explore how the administration of oxytocin to patients with schizophrenia affects neural activity and performance.

Chapter 7 will provide a general discussion of the findings from Chapters 3 to 6.

Hypotheses:

In general, I hypothesise that both patients with schizophrenia and healthy controls who have taken a placebo will be biased toward choosing a happy face even when the

evidence supports the angry face as a better choice. This bias will be attenuated by ropinirole, amisulpride and oxytocin. Furthermore, this attenuation in bias will be accompanied by changes in neural activity where ropinirole will act to augment neural activity in regions associated with decision-making, reward and social processing which have dopaminergic ties and amisulpride will act to attenuate neural activity in these regions. As the majority of the patients with schizophrenia in this study were medicated using dopamine antagonists, changes in neural activity in the patients will most closely resemble healthy controls who were administered amisulpride and will demonstrate an attenuation of neural activity in regions associated with decision-making, reward and social-processing. Additionally, attenuation of bias toward choosing the happy face after oxytocin administration in patients with schizophrenia will be accompanied by the attenuation of neural activity in regions associated with social processing.

Furthermore, as emotionally valenced faces are through to be more salient than neutral faces, it is thought that, in general, more changes will be seen when deciding between emotionally valenced faces than neutral faces and that this will be the most evident in regions associated with social processing such as the amygdala.

CHAPTER 2 - METHODS AND MATERIALS

2.1 PARTICIPANTS

2.1.1 STUDY USING DOPAMINERGIC MANIPULATION

Forty-eight right-handed patients diagnosed with schizophrenia and schizoaffective disorder as categorised by the International Classification of Diseases -10 (ICD-10, 1992) (33 males) and twenty-seven matched healthy controls (22 males) were recruited for the main study exploring how dopamine affects decision-making. Of the 27 healthy controls, 14 participants did not complete all three scanning sessions leaving a final sample of 20 healthy controls (17 males) and 42 patients with schizophrenia (39 males). Healthy controls and patients with schizophrenia were matched in terms of age, gender, handedness and socioeconomic background as determined using parental occupation in the National Statistics Socio-Economic Classification (Rose, 2001). Intelligence quotient (IQ) was measured in all participants using the two-item Wechsler Abbreviated Scale of Intelligence (WASI) consisting of the vocabulary and matrix reasoning subtests (Wechsler, 1999). IQ was lower in the patients with schizophrenia than in the healthy controls ($t(60) = 2.548$, $p = 0.013$). Further demographics are listed in Table 2.1.

Diagnosis of the patients with schizophrenia was confirmed by assessment of case notes and by correspondence with each individual's consultant psychiatrist. To assess symptom severity, patients with schizophrenia were also assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Duration of illness for the patients with schizophrenia was 13.5 ± 8.8 (mean ± standard deviation).

Forty patients with schizophrenia were taking anti-psychotic medication throughout the course of the study and two patients with schizophrenia were stable off of their medication for a duration of over six weeks [olanzapine (n =11), quetiapine (n = 2), haloperidol (n = 1), aripiprozole (n = 4), amisulpride (n = 2), risperidone (n = 3), modecate (n = 1), risperidol consta (n = 2), clopixol (n = 3), clozapine (n = 14), piportil (n = 1)]. Chlorpromazine equivalents were calculated for all patients with schizophrenia using conversion tables (Chue et al., 2005; Lehman et al., 2004; Nayak et al., 1987; Schooler and Levine, 1976; Woods, 2003). Patients with schizophrenia were recruited though local national health trusts. Healthy controls were recruited using local advertising.

Healthy controls were excluded if they: had any previous history of mental or neurological illness or if any first degree relatives suffered from any previous psychotic illness. Participants from both groups were excluded if they: exhibited any significant visual or hearing impairments; suffered from any neurological disorders; reported any drug dependencies over the last 6 months. Patients with schizophrenia were all stable on their current medication. Healthy individuals also provided urine samples on each day of testing to screen for the use of cannabis, cocaine, opiates, amphetamines and benzodiazapines. All urine samples were negative for those included in the study. Female participants were also required to provide a negative pregnancy test prior to being administered fMRI scanning.

Ethics were obtained from the Central London Research and Ethics Committee 1. All participants gave informed written consent and were compensated for their time and travel.

2.1.2 STUDY USING OXYTOCIN

In our second experiment, 20 right-handed, male patients with schizophrenia and schizoaffective disorder as categorised by the (ICD-10, 1992), taken from the first study, were included in a double blind crossover study using oxytocin and a placebo. The mean age was 37.9 ± 7.4 (mean ± standard deviation). The patients with schizophrenia included in this study did not significantly differ from the patients in the previous study in any categories aside from gender as no females were included in this study. Further demographic details can be found in Table 2.1.

Nineteen patients with schizophrenia were taking anti-psychotic medication throughout the course of the study [olanzapine (n = 10), risperidone (n = 2), modecate (n = 1), clopixol (n = 1), clozapine (n = 3), haloperidol (n = 1)]. Chlorpromazine equivalents were calculated for all patients with schizophrenia using conversion tables (Chue et al., 2005; Lehman et al., 2004; Nayak et al., 1987; Schooler and Levine, 1976; Woods, 2003).

Ethics approvals were obtained from the Camberwell and St Giles Research Ethics Committee. All participants gave informed written consent and were compensated for their time and travel.

TABLE 2.1 - Demographics and clinical sample characteristics

	Dopamine Study		Oxytocin Study		
	Healthy Volunteers (N=20) (mean (SD))	**Patients with schizophrenia** (N=42) (mean (SD))	**Patients with schizophrenia** (N=20) (mean (SD))	**Statistics between patient groups**	**Statistics between groups for dopamine study**
Age (years)	36.25 (9.41)	37.36 (8.82)	37.90 (7.43)	t(60) = 0.238, *p* = 0.813	t(60) = 0.452, *p* = 0.653
WASI IQ	107.30 (14.42)	97.10 (14.89)	98.85 (13.24)	t(60) = 0.449, *p* = 0.655	t(60) = 2.548, *p* = 0.013*
Parental occupation (NS – SeC)	2.35 (1.60)	2.79 (1.63)	2.80 (1.70)	t(60) = 0.032, *p* = 0.975	t(60) = 0.989, *p* = 0.326
Gender	18M, 2F	33M, 9F	20M	$\chi^2(1) = 5.013$, *p* = 0.025*	$\chi^2(1) = 0.359$, *p* = 0.735
Age at onset (years)	-	23.76 (5.80)	24.50 (6.48)	t(60) = 0.452, *p* = 0.653	
Duration of illness (years)	-	13.54 (8.76)	13.40 (6.53)	t(60) = 0.062, *p* = 0.951	
CPZ equivalents (mg/day)	-	473.93 (393.15)	430.05 (236.27)	t(60) = 0.460, *p*= 0.647	
PANSS	-				
Positive Symptoms	-	16.18 (4.37)	14.95 (4.97)	t(60) = 0.977, *p* = 0.332	
Negative Symptoms	-	18.28 (5.48)	18.30 (4.99)	t(60) = 0.017, *p* = 0.986	
General Symptoms	-	31.13 (6.95)	30.70 (7.10)	t(60) = 0.222, *p* = 0.825	
Total	-	65.58 (13.89)	63.95(14.65)	t(60) = 0.419, *p* = 0.676	

SD = Standard deviation

IQ = Intelligence quotient; M = Male; F = Female.

WASI = Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999)

NS - SeC = National Statistics Socio-economic Classification (Rose, 2001)

CPZ = Chlorpromazine equivalent (Woods, 2003)

PANSS = Positive and Negative Symptom Scale (Kay et al., 1987)

*significant at $p < 0.05$

2.2 PHARMACOLOGICAL PROBES

2.2.1 DOPAMINERGIC PROBES IN HEALTHY CONTROLS

Healthy controls were administered a dopamine agonist (ropinirole (0.25mg)), dopamine antagonist (amisulpride (400 mg)) or a placebo (ascorbic acid) in a double-blind crossover design. The order of each drug administration was counterbalanced across testing days. All drugs were encapsulated and packaged by the South London and Maudsley (SLaM) pharmacy and administered on the same day.

Patients with schizophrenia were not given any medication supplement to any that they were currently taking. It was decided not to dose them with a placebo as this would introduce potential confounders secondary to the medication that they were already taking. As this study included patients under many varieties of medications, it was deemed too difficult to separate out effects from taking a placebo in addition to parsing out any effects of long term-medication. Furthermore, even the subjective experience of being told they are receiving a placebo is capable of introducing differences in performance and neural activity (de la Fuente-Fernández et al., 2001; Moerman and Jonas, 2002).

2.2.1.1 AMISULPRIDE PHARMACOKINETICS

Amisulpride was used as a dopamine antagonist in this study. It was chosen due to its high affinity for dopamine D_2/D_3 receptors (Green, 2002) as well as its efficacy in treating the negative symptoms of schizophrenia (Boyer et al., 1999). At low doses (50-100 mg), amisulpride is disinhibitory and preferentially blocks presynaptic dopamine synthesis. At higher doses (>200 mg) amisulpride has a higher D_2-receptor postsynaptic occupancy and antagonism (Green, 2002). There are two distinct absorption peaks

occurring at approximately 1 and 4-5 hours (T_{max}) after administration (Kudris et al., 2011) (Figure 2.1).

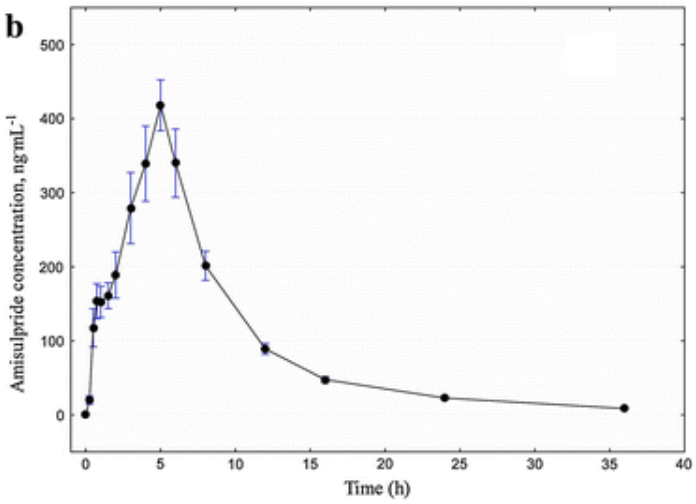

FIGURE 2.1 - Pharmacokinetic profile of amisulpride showing the test solution concentration in the plasma with a peak at 1 and 4-5 hours post administration (Kudris et al., 2011)

2.2.1.2 ROPINIROLE PHARMACOKINETICS

Ropinirole is an indole (or non-ergot) derived dopamine agonist whose chemical name is 4-[2-(dipropylamino)ethyl]-1,3-dihydroindol-2-one. It was chosen for this study due to its high affinity for D_2/D_3 receptors. It is most commonly used for the treatment of Parkinson's which is a disorder caused by a deficiency in dopamine (Alonso Cánovas et al., 2014). It is rapidly absorbed and reaches its maximum concentration in 1 to 2 hours which is increased by 1 to 2 hours if taken with food. However, greater increases in absorption rates are seen with increases in the fat content of food (Brefel et al., 1998) (Figure 2.2).

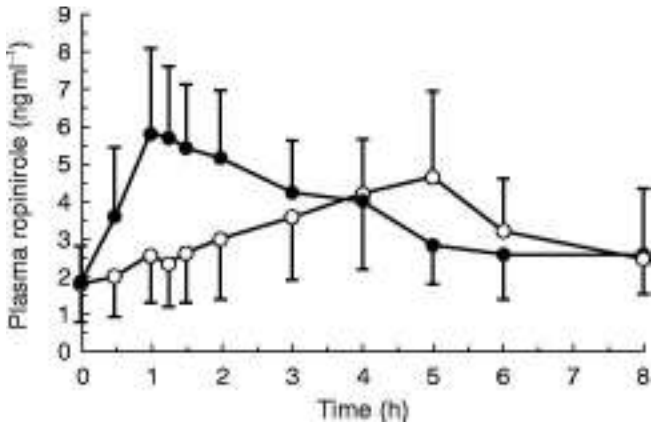

FIGURE 2.2 - Pharmacokinetic profile of ropinirole showing the concentration in the plasma with a peak at 1-2 hours (black dots) the white dots represent plasma concentration after receiving a meal with an extremely high fat content (64g of fat) (BREFEL ET AL., 1998).

2.2.2 OXYTOCIN IN PATIENTS WITH SCHIZOPHRENIA

In our second experiment, patients with schizophrenia were administered an oxytocin nasal spray (Syntocinon, Switzerland, 40 IU) or a matched nasal spray containing all the same inert ingredients as the oxytocin spray. All sprays were purchased through Mawdsley Brooks & Co. and manufactured by Delpharm. Both the oxytocin and placebo spray contained glycerol, sorbitol, sodium chloride, citric acid, chlorobutanol hemihydrate, disodium phosphate, methyl parahydroxybenzoate, propyl parahydroxybenzoate and water.

The pharmacokinetics of intranasal oxytocin have yet to be fully established. Currently only one study to date has explored how intranasal oxytocin administration affects oxytocin levels within the cerebrospinal fluid (CSF) over time in order to determine its peak effects within the CSF and plasma (Striepens et al., 2013). They found that although oxytocin levels in the plasma increased after only 15 minutes, no significant increases in CSF oxytocin levels were observed until 75 minutes post administration. However, the sample size was extremely small (1 on placebo and 3 on oxytocin) and no further time points were recorded so it hard to draw conclusions on whether these

findings would extend to a greater population and how long oxytocin in the CSF would remain elevated. A similar study in humans using a related neuropeptide, vasopressin, has formed the basis for current timings in many oxytocin studies and have shown that levels were increased in the CSF compared to a placebo were significantly increased as soon as 10 minutes post–administration up to at least 2 hours after administration (Born et al., 2002) suggesting that the effects of oxytocin in the CSF may also be longer lasting. Furthermore, even though plasma levels of oxytocin have not been found to correlate with levels in the CSF (Kagerbauer et al., 2013; Striepens et al., 2013), the literature suggests that oxytocin administration can result in elevated levels of plasma oxytocin for up to 7 hours, with oxytocin levels up to 10 times greater than in the placebo condition (van Ijzendoorn et al., 2012) and that, in rodents, CSF oxytocin levels are almost immediately elevated following intranasal administration and can remain elevated for up to 90 minutes in the amygdala and hippocampus (Neumann et al., 2013).

Current fMRI challenge studies, beginning with the paper by Kirsch et al. (2005) have been primarily based on the earlier findings from Born et al. (2002) looking at how plasma levels and CSF levels of the neuropeptide vasopressin are elevated at earlier time points than in the study by Striepens et al. (2013) and scanning times have accordingly generally begun 30 to 45 minutes post- oxytocin administration (Domes et al., 2007b; Kirsch et al., 2005; Kosfeld et al., 2005; Wittfoth-Schardt et al., 2012). Given that these studies using this timeframe have shown an effect of oxytocin administration on neural activity, oxytocin administration in this study was timed to be 30 minutes before participants were put in the MRI scanner and 45 minutes before the start of the first task within the scanner. However, the first task administered in the

scanner does not form part of this thesis. The task used here was performed second after approximately 45 minutes performing the other task at a time of approximately 90 minutes post-administration.

2.3 DRUG ADMINISTRATION

2.3.1 DOPAMINERGIC PROBES

For the double-blind dosing of our participants, ropinirole (0.25 mg), amisulpride (400 mg) and the placebo (ascorbic acid) were all self-administered orally by our participants. For each session, each dose was placed in a plastic cup in front of the participant alongside a cup of water. They were asked to swallow the pill and follow this with a drink of water. We ensured that the participants did not touch the pills so that they could not distinguish between any of the medications encapsulated within. Additionally, the pharmacy took great care to ensure that each capsule appeared qualitatively similar to also keep the capsules from being visually discriminated. This procedure was repeated twice each day with one capsule corresponding with the time frame for either amisulpride or ropinirole to reach T_{max} at scanning time such that the first administration was timed four hours before the scan (to coincide with the T_{max} of amisulpride) and the second administration was timed two hours before the scan (to coincide with the T_{max} of ropinirole). Additionally, as fatty acids can affect the T_{max} of ropinirole, fatty acid intake was restricted for all participants on the day of the scan.

2.3.2 OXYTOCIN NASAL SPRAY

In our second experiment, both the oxytocin (40 IU) and placebo nasal sprays were self-administered by our participants. Each spray was manufactured to appear qualitatively similar so that neither the participant nor tester had any knowledge which

spray was being administered. Nasal sprays were administered following the guidance outlined by Guastella et al. (2013). First each spray was primed so that it was spraying full sprays each time it was pumped. Each participant was told to tilt their head back at a slight angle and insert the nasal spray into one of their nostrils while trying to keep the spray bottle as upright as possible. They were then told to push down on the pump action while simultaneously inhaling through their nostrils as deep as possible while also blocking the opposing nostril with their other hand. They were then asked to switch nostrils and repeat this administration. A break of 45 seconds was given between each administration to allow for the nasal spray to allow the nasal spray to be absorbed by the nasal cavities. Proper administration was demonstrated to each participant before self-administration albeit without the actual insertion and spraying of the agent. Each spray was acquired on the day of administration from the South London and Maudsley pharmacy, approximately one hour before being administered to ensure an adequate storage temperature was not been breached before administration.

2.4 TASK

The task used was a forced-choice, stochastically rewarded decision-making task incorporating elements of social valence. This task has been developed and tested extensively by ourselves over the last few years, and we have used it to show how social information (provided by different facial expressions taken from the Ekman series (Ekman and Friesen, 1971)) can guide decision making processes (Averbeck et al., 2012; Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2010; Evans et al., 2011b; Furl et al., 2012). Before beginning the task, subjects were all given the following instructions:

> "The next task is the task we practiced outside the scanner with the two different faces.
>
> You will be presented with two faces on each side of the screen, each with a different probability of winning. Your job is to work out during each block which face has the highest chance of winning and to continue to pick the face that you think is winning the most often. Remember, if the face you pick loses, the other face would have won.
>
> Also, keep in mind that at the beginning of each block, the chances of each face winning will be reset. You will be told each time a new block will begin.
>
> The faces are positioned side by side so to select the face on the left press with your index finger. Can you do that now please? To pick the face on your right, press with your middle finger. Can you do that for me now please?
>
> Great, any questions before we begin the task?."

Thus, their aim is to try and determine through trial and error which face has the highest probability of winning on any given trial and to pick that face, so as to maximize their reward (number of wins). In each trial two faces were presented to the left and the right of the screen. Pairs consisted of either: a happy face and an angry face of the same identity, or of two neutral faces of differing identities see Figure 2.4 for examples of each stimulus pair. Stimulus pairs were alternated so that one block consisting of pairs of emotionally valenced stimuli (i.e. happy and angry faces) was alternated with a block consisting of pairs of neutrally valenced stimuli (i.e. neutral faces). Each visit consisted of two scanning sessions comprised of four blocks of stimuli each presented in the counterbalanced manner described above. Each block consisted of 30 trials with the presentation of each face counterbalanced across the left and right sides. Participants selected a face using the button box and were then told whether they had won or lost on that trial. A 'win' corresponded to 10p being added to the total winnings, a 'loss' meant that nothing was added. Participants were told that

they would all receive a fixed amount and that the money they "earned" in the task is fictitious. Although the money did not affect the overall earnings of the participants, the financial incentive still helped to ensure that participants engage with the task. Over each block, each face is rewarded according to a predetermined probability. Unbeknownst to the participants, one face is rewarded 40% of the time, the other 60%. Reward probabilities remained constant for each block of 30 trials and were then reassigned. The probabilities of each face winning was counterbalanced across blocks such that the angry face won more in half of the blocks and the happy face won more in the other half, and that identity one won more over identity two for half of the blocks. The order of these wins was counterbalanced across the participants and visits. Timings and presentation of the stimuli presented are listed in Figure 2.3. The different facial stimuli used are presented in Figure 2.4. This task was run immediately after the structural and localiser scans were complete in Chapters 3 and 4 and after another task not described in this thesis in Chapter 6.

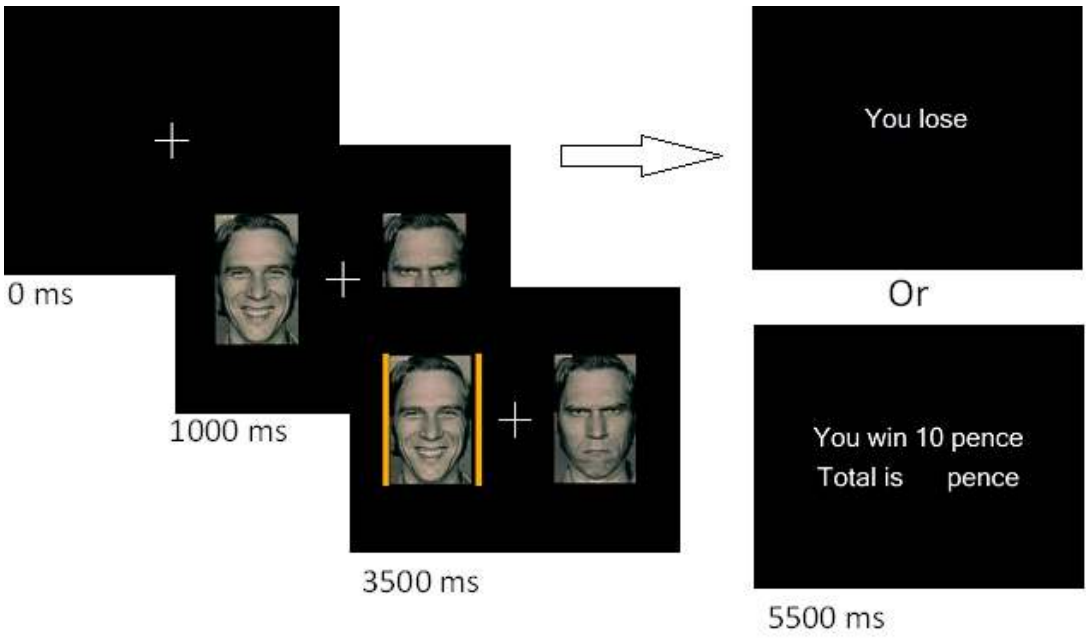

FIGURE 2.3 - Task design for the decision-making task in the scanner

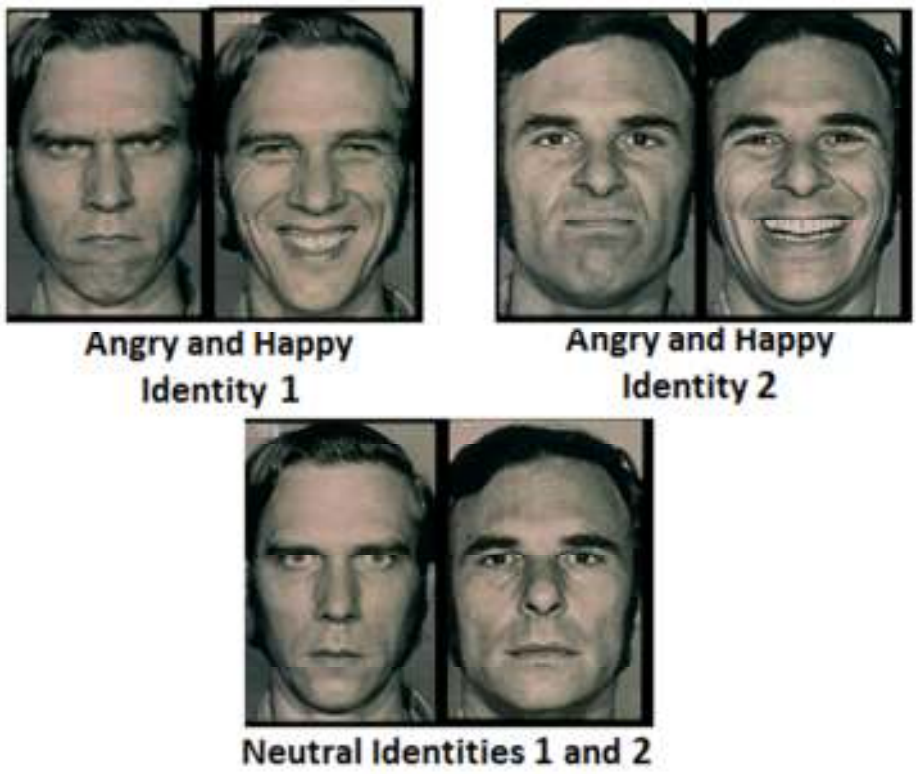

FIGURE 2.4 - Facial stimuli used for decision-making task in the scanner

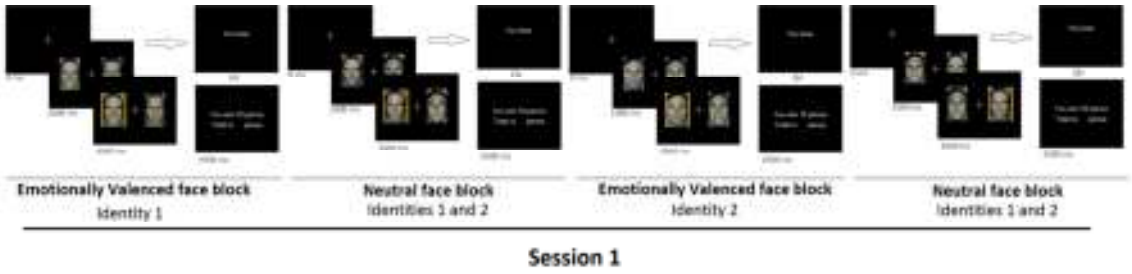

FIGURE 2.5 - Example of a session layout for the decision-making task in the scanner

Other tasks were also run in the scanner for both experiments but will not be discussed in this thesis. We expect to publish these results elsewhere.

2.5 BEHAVIOURAL DATA ANALYSIS

2.5.1 ASSESSING THE PROBABILITY EACH FACE WILL BE REWARDED

Participants were told that they needed to pick which face was winning the most often from a set of two faces either both a happy and an angry face of the same identity, or from two neutral faces of different identities. Participants were not given any prior

information on which face would likely win any given trial, from a purely probabilistic standpoint, participants should view both faces in the first instance with an equal probability of winning. This represents a flat prior for the start of each trial centred at 0.5 or (50%). For any proceeding trials, participants should be able to work out the relative probability of a win based on previous feedback. Overall, the probability of each face winning will represent a split of 0.6 to 0.4 (i.e. 60% to 40%); however, due to the nature of the game, the probability that any one face may be winning at any point in time may be different to the overall probability. Thus, in the short term, the face that is least probable to win over the whole block may have a higher probability of winning at an earlier trial. To take this into account, an ideal observer was calculated to determine the optimal face to pick on a trial by trial basis based on current feedback. Performance of each individual was referenced to this observer to determine if they were picking the optimal face, in terms of which had the highest probability of being rewarded, as well as to determine if they were biased toward either face. This probability for each face was calculated as:

$$p(\theta_i) = \frac{q_i + z_i}{n_{trials}}, \quad i\text{=happy face or neutral identity 1}$$

$$p(\theta_j) = \frac{q_j + z_j}{n_{trials}}, \quad j\text{=angry face or neutral identity 2}$$

Where Θ_i represents the probability that either the happy face or neutral face with identity 1 (*i*) will be rewarded and Θ_j represents the probability that the angry face or identity 2 (*j*) will be rewarded; q_i represents the number of times a face has been chosen and has been rewarded (i.e. the happy or angry face or either of the neutral face identities); z_i represents the number of times the chosen face would have won but

the other face was chosen and lost; n_{trials} is the number of current valid trials. Both probabilities were summative to 1 such that probability for the angry face, or neutral identity 2, could also be calculated as $1 - p(\Theta_i)$. Performance was deemed optimal if the face picked had a probability of winning greater than or equal to 0.5 such that the choice of the ideal observer ($f(\Theta)$):

$$p(\Theta_i > \Theta_j) > 0.5,\ f(\Theta) = i$$

$$p(\Theta_j > \Theta_i) > 0.5,\ f(\Theta) = j$$

2.5.2 ASSESSING REWARD PREDICTION ERROR (RPE)

From these estimates a reward prediction error (RPE) was also determined. RPE measures the difference between the actual reward and the probability of being rewarded as calculated by the model. It is calculated as follows:

$$\text{RPE}(t) = r(t) - p(r(t))$$

Where $r(t)$ represents the reward received on trial t of either 1 (yes rewarded) or 0 (not rewarded) and $p(r(t))$ represents the probability of being rewarded for whichever face was chosen on trial t and was determined using the probabilities listed in the previous section. This can also be thought of as the reward received (0 or 1) minus the probability of the reward predicted.

2.5.3 ASSESSING BIAS TOWARD ONE OF THE FACES

Bias was looked at by measuring the number of times each participant picked the face that was not currently supported by the ideal observer. Thus, to assess how facial expression, or identity, biased decision-making, all trials were separated into when participants agreed with the ideal observer and when they disagreed with the ideal observer for each facial valence as well as for the two neutral face identities. A 2x2

contingency table was calculated for each block type (i.e. emotionally valenced and neutral) representing choices by the ideal observer and choices by the participant. When the probability for each face winning was ambiguous (i.e. equal probabilities for both faces), the contingency count for each face (*HH, AA*) was increased by 0.5.

TABLE 2.2 - Contingency table example for emotionally valenced faces

		Ideal Observer choice	
		happy face	angry face
Participant choice	happy face	*HH*	*HA*
	angry face	*AH*	*AA*

Using this table it was possible to calculate the conditional probability of each participant choosing the happy face when they should have chosen the angry face given the current evidence for the angry face $p(\text{happy}|\text{angry})$ as well as when they chose the angry face when they should have chosen the happy face given the current evidence for the happy face $p(\text{angry}|\text{happy})$. For the happy faces, this was calculated as the times they chose the happy face when they should have chosen the angry face over the total number of times the happy face was chosen or:

$$p(\text{happy}|\text{angry}) = \frac{HA}{HA + AA}$$

And for the angry face this was calculated as the times they chose the angry face when they should have chosen the happy face over the total number of times the angry face was chosen or:

$$p(\text{angry}|\text{happy}) = \frac{AH}{AH + HH}$$

It is important to note these measures are not calculated in the same way as talked about in section 2.5.1 assessing the general probabilities of being associated with a reward. The difference between these two measures looking at bias was calculated to

represent the degree of bias toward picking the happy face *p*(happy|angry) - *p*(angry|happy). This is a measure of conditional probability given both the observed and expected choice. This measure indicates how often participants ignore the evidence that has accumulated for the negatively valenced face and chose the positively valenced face compared to how often they ignored evidence that had accrued for the positively valenced face and chose the negatively valenced face. This bias distribution was examined across all participants and entered into a one sample t-test to see if it significantly differed from 0. This process has been replicated in multiple studies to represent the degree of bias (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2010; Evans et al., 2011b; Furl et al., 2012). This process was also repeated for the two neutral face identities to see if participants favoured either of these faces.

4.2 FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)

Functional Magnetic Resonance Imaging (fMRI) was used in this study as an indirect measure of neural activity in each of our participants. It is generally accepted that increased neural demand causes an increase in blood flow to regions of the brain which are neurally active. fMRI works by measuring small signal changes in the brain due to increased blood flow to different regions of the brain. In the late 1990's, it was observed that deoxygenated haemoglobin (molecules in the blood which carry oxygen) was affected differently in a magnetic field than oxygenated haemoglobin (Ogawa et al., 1990). They observed that haemoglobin becomes strongly paramagnetic in a deoxygenated state and thus, when introduced to a radiomagnetic pulse, the signal decays more rapidly than oxygenated haemoglobin causing areas with oxygenated blood to appear "brighter". Thus oxygenated blood works as a natural contrast agent

to regions of the brain with increased localized blood flow and is referred to as the blood oxygenation level-dependent (BOLD) signal (Logothetis, 2008).

2.6 IMAGE ACQUISITION

Functional magnetic resonance imaging (fMRI) data for both experiments were acquired on a Discovery MR750 3T scanner at the Centre for Neuroimaging Sciences, London (T2* weighted gradient-echo echo-planar images (EPIs), repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, flip angle = 75°, 64 x 64 matrix, 24cm field of view). A 12-phase head coil array was used over the whole head for RF transmission and reception. Each whole-brain image contained 38 3-mm axial slices separated by a distance of 0.3 mm with in-plane isotropic voxel resolution of 3.75 x 3.75 mm. For each session, 430 scans were acquired and two sessions were recorded for each participant.

Before the behavioural portion of the experiment, a T1-weighted structural scan using a fast-spoiled gradient-echo pulse sequence (TR = 9.356 ms, TE = 3.828 ms, flip angle = 12°, time to inversion = 450 ms) was acquired for reference purposes. The first four volumes were discarded to allow for transient effects.

For the study looking at dopaminergic manipulation in healthy controls and the differences to patients with schizophrenia, participants made their responses using a two buttons on a three button-box in the index and middle fingers of their right hand. The third button was for an additional task which will not be analysed in this thesis. For the study using oxytocin administration, only a two button-box was used. Participants also made their choices with the index and middle fingers of their right hand. Head movement was minimised using headphones and additional padding around the head and ears as well as around the arms and legs.

2.7 IMAGE ANALYSIS

All data were preprocessed and analyzed using Statistical Parametric Mapping 12 (SPM12) (Wellcome Department of Imaging Neuroscience, London, UK. www.fil.ion.ucl.ac.uk/spm) and MATLAB R2014a (MathWorks Inc. Sherbon, MA, USA). First, each structural image was reoriented to set the point of origin at the anterior commissure and the degree of rotation was set to match the posterior commissure. Each structural image from the first visit of each subject was segmented into various tissue classifications and then smoothed slightly. Segmentation allows for each subject's brain to be spatially normalised to a standard space and allows grey matter to be matched between subjects and reduces non-brain structural variability on the registration. Further preprocessing comprised spatial realignment to the first image of the first session where each image is realigned using a least squares approach and a six parameter (rigid body) spatial transformation (Friston et al., 1995) which helps with the removal of movement artefacts by realigning each image to the same native space. Next each image was resliced to match the first image voxel-for-voxel. Then each session was coregistered to the mean image of each session and the T1-weighted structural image, forward deformations from the segmentation process were used to normalise the images to a standard template of the Montreal Neurological Institute (MNI) brain, finally all the images were smoothed using an 8-mm full-width at half-maximum Gaussian kernel to reduce noise and residual differences in functional and gyral anatomy between subjects. Images were analysed using an event-related general linear model (GLM). Onsets were modelled at each task event using a delta (stick) function.

Events of interest in the GLM included the presentation of the faces, a decision-making regressor indicating when the decision was made for which face the subject believed would be rewarded (determined by a button press), and the feedback presentation of whether the subject received a reward or not within each trial. Also modelled were regressors to represent the motion parameters as well as parametric modulators on the decision-making and feedback regressors. The decision-making regressor was parametrically modulated by the probability that the face they picked would win. The calculations used to determine this probability are outlined on page 47. The feedback regressor was parametrically modulated by the reward prediction error (RPE) determined by subtracting the actual reward from the predicted probability the face the participant chose would win, as detailed on page 49. Each regressor, except for the motion parameters, was convolved with a canonical hemodynamic response function and its temporal derivative.

The contrasts for each chapter focussed on outputs from the decision-making and RPE regressors for between group and drug analyses. Further details on the contrasts for each chapter are outlined in each chapter.

Contrasts were whole brain cluster-level family wise error (FWE) corrected at $p<.05$ with a height threshold of $p < .005$, uncorrected, and an extent threshold of 100 contiguous voxels. Voxels which survived peak level family wise error correction at $p<.05$ are also reported. When looking at the main effect of task and emotion in the placebo condition, cluster level results are reported at a more stringent height threshold of $p < .001$. Reported voxels coordinates were converted from Montreal Neurological Institute (mni) coordinates into Talairach coordinates using the function icbm_spm2tal (Laird et al., 2010; Lancaster et al., 2007a) and were entered into

Talairach Daemon to confirm their location in gray matter (Lancaster et al., 1997; Lancaster et al., 2000). Questionable results were further visualised by entering the original mni coordinates into xjview (http://www.alivelearn.net/xjview). Results are reported as their original mni coordinates as output by SPM12.

Region of interest analyses were also carried out within regions with an *a priori* interest to the study. Volumes of interest were defined using WFU PickAtlas Tool (Maldjian et al., 2003) for the amygdala and striatum and the ventral striatum was taken from Mawlawi et al. (2001).

Effect sizes were also calculated for all two-sample and paired t-tests to assess the strength of each finding. The effect size is a dimensionless number which facilitates the integration of findings across studies that used different types of measurements. The choice of effect size estimator is a much debated and still unresolved issue (Hunter and Schmidt, 1990) and is related to the choice of whether or not greater reliance should be laid on studies carried out on larger samples when the effect size is to be computed. We chose to use an effect size estimator corrected for the number of subjects included in each study using Cohen's d statistic (Cohen, 1992). Guidelines for calculations were followed using Thalheimer and Cook (2002)'s method. By examining effect sizes rather than statistical significance, we can better understand what differences exist in the general population and whether these differences might merit further study. Effect size (d) is taken to mean "the degree to which a phenomenon is present in the population" (Cohen, 1988); d was indexed according to Cohen's scheme (Cohen, 1992). Cohen placed the value of d for small effects at 0.2, for medium effects at 0.5, and for large effects at 0.8.

CHAPTER 3 - THE NEURAL CORRELATES OF DECISION-MAKING DURING AN ASSOCIATIVE LEARNING TASK WITH A SOCIAL COMPONENT – THE EFFECTS OF DOPAMINERGIC MANIPULATION IN HEALTHY PARTICIPANTS

3.1 BACKGROUND

Decision-making results from a complex interplay between our internal thoughts and preferences and their interactions with the world around us. Differences in the evaluation of the world lead to the differences in decisions an individual makes. An important aspect of this evaluation is determining the potential outcomes of any actions and, specifically, the value that these outcomes hold. For example, when trying to determine what to order on a menu, generally a person will evaluate each option and assign it with an implicit value. The option a person will pick from the menu is the one that holds the highest implicit value to them. One person may value price over taste and thus will pick the cheapest item while another may value quantity and will pick the greatest serving size and yet another may value taste and pick the item they deem the tastiest. How we assign these values to particular items internally and subsequently interpret them to generate an action is driven by an important neurotransmitter called dopamine (Schultz, 2006, 2007; Smith and Huettel, 2010; Wise and Rompre, 1989). It has been suggested that, dopamine aids in both the formation, or the conceptualisation of value in terms of the costs and benefits of a given option or set of options, and updating, or re-evaluation, of predictions about rewards (Schultz, 2006), for example, how much value we could expect from picking from a set of options like a menu. By altering the incentive salience, or the implicit degree of desirability, or "wanting," of an object (Berridge, 2007), and updating how future rewards are represented internally (Schultz, 2013), dopamine is believed to contribute

to value formation and motivational behaviour. Incentive salience spurs behaviour by attributing a higher value to certain salient stimuli that stick out amongst competing stimuli, and in turn also contributes to determining which events are important enough to be encoded in memory. An example could be the marketing of a new menu item through flashy advertising designed to make it look like it tastes better and/or substantially discounting the price to make it a more salient option. The degree to which these stimuli are more salient than other stimuli in the environment and the relative rewards received from picking these stimuli are thought to be updated based on dopaminergic outputs. Both negative feedback, in the form of punishments or less desirable outcomes, and positive feedback, or rewards from more desirable outcomes, help to update relative values of stimuli. Negative feedback induces a reduction in dopaminergic firing and positive feedback induces increased dopaminergic firing (Schultz et al., 1997) (Figure 3.1). The degree to which dopamine neurons fire in response to feedback is mediated by the anticipated reward amount combined with the feedback received. If a high reward is expected and a high reward is received there will be little dopaminergic activity because the difference between the actual reward and the anticipated reward is negligible. However, if a high reward is expected and no reward is received, this negative feedback should induce a greater reduction in dopaminergic firing than if no reward had been expected (Schultz, 1998; Schultz et al., 1997). This firing in relation to the difference between reward received and anticipated reward is known as the reward prediction error (RPE) signal and has been well established (Berridge, 2012; Colombo, 2014; Glimcher, 2011; Hart et al., 2014; Hollerman and Schultz, 1998; Lak et al., 2014; Murray et al., 2008; Philiastides et al., 2010; Poore et al., 2012) and can even encode the variance in the signal as well (Friston et al., 2012). In behavioural terms, positive outcomes, or rewards would be

encoded as events which would lead to reward in the future whereas aversive outcomes, or those which do not fulfil our expectations would be encoded as events to avoid in the future. Given the high concentration of dopamine neurons in the striatum, these signals have generally been found in the ventral striatum close to the substantia nigra and ventral tegmental area. Further encoding of incentive salience and overall value of a choice generally correlates with signals in a network of areas including the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) (Botvinick, 2007; Devinsky et al., 1995; Matsumoto et al., 2007).

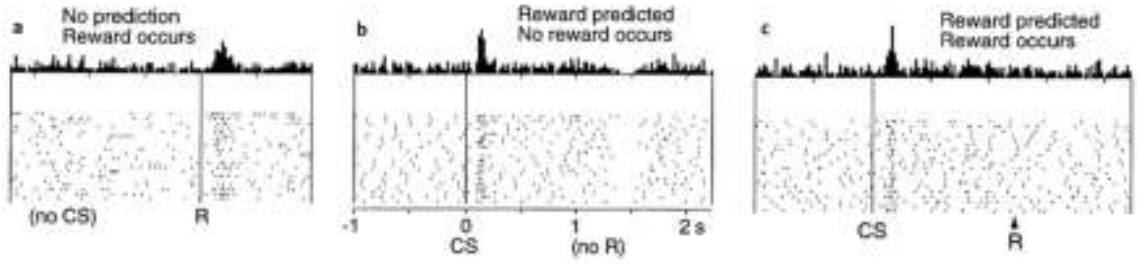

FIGURE 3.1(a-c) - Examples of neural response to reward in the striatum, where CS represents a conditioned stimulus and R represents where a reward was given or not given. Taken from (Schultz, 1998). a) The higher concentration of dots after the reward stimulus are indicative of greater firing of dopaminergic neurons in the striatum after receiving a reward with no conditioned stimulus. b) Dopamine neurons fire after the conditioned stimulus associated with a reward but when no reward is given, this is also accompanied by a reduction of dopaminergic neurons firing in response to the conditioned stimulus and lack of the associated reward. c) Once the dopaminergic neurons are conditioned to expect a reward and a reward is given, dopaminergic neurons only fire in response to the stimulus which indicates a reward will be given.

However, given that incentive salience also affects dopaminergic signalling, the predicted reward can be altered by the incentive salience determined by behavioural or social biases. This is notable in social situations where the same face may take on a higher social salience based on its emotional valence, known as affective priming (Murphy and Zajonc, 1993). A smiling face is more likely to be regarded as salient amongst a series of neutral faces as would be an angry face amongst neutral faces. The difference is that the smiling face will generally be associated with a more positive

value and it is more likely that viewing a happy, or smiling, face will facilitate cooperation (Mussel et al., 2013; Scharlemann et al., 2001). In fact, people are even willing to forego the chance of a monetary reward just to see a genuine smile (Shore and Heerey, 2011); whereas prior experience will bias most people to associate angry faces with more negative interactions and has been shown to decrease cooperative interactions (Mussel et al., 2013). Furthermore, in a task which presented different emotionally valenced faces to people before asking them to pour and consume a drink, people who viewed happy faces first increased the amount of a beverage poured and consumed and made participants more willing to pay for their drink while viewing angry faces first had the opposite effect (Winkielman et al., 2005). This shows that emotionally valenced faces can also have an unconscious effect on our actions.

The use of dopamine agonists and antagonists offers a way of manipulating dopaminergic binding in the brain and to examine the association between dopaminergic activity and neural activity during cognitive tasks. Previous studies using dopaminergic manipulation in healthy controls have generally modelled the response to reward related stimuli using prediction errors (RPEs) and value related functions of processing decisions. These studies used similar decision-making paradigms during which subjects were presented with two choices with varying probabilities of being rewarded. They were then asked to pick the option that they believed was more likely to be rewarded. The first study by Pessiglione et al. (2006) found that giving L-DOPA, a dopamine agonist, made subjects more likely to choose the more rewarding option compared to subjects who received the dopamine antagonist, haloperidol. Additionally, these choices were accompanied by modulation of neural activity within the striatum where L-DOPA administration enhanced neural activity, correlating with

RPE in the striatum relative to haloperidol. Additionally, two further studies that used L-DOPA and haloperidol, albeit without the same reward-based probabilistic decision-making paradigm, found that, during somatosensory decision-making L-DOPA, haloperidol and a placebo modulated behavioural and neural effects L-DOPA enhanced neural activity within the primary sensory cortex and haloperidol attenuated neural activity within this region (Pleger et al., 2009). Interestingly, this study did not find a significant drug effect within the striatum. The other study also used an L-DOPA, haloperidol and a placebo but presented their subjects with subliminal sexual images which required no decision-making. They found that neural activity within the dorsal anterior cingulate (dACC) and nucleus accumbens was enhanced by L-DOPA and attenuated by haloperidol, suggesting that these regions also respond to subconscious sexual reward which is modulated by dopaminergic binding (Oei et al., 2012). Together, these three studies show that the dopamine agonist L-DOPA appears to increase neural activity in areas related to reward, which are have high dopaminergic receptor densities and decrease neural activity with the dopamine antagonist haloperidol in these same regions.

However, in another study run by Bernacer et al. (2013) dopamine agonists were found to disrupt decision-making. They used methamphetamines as a dopamine agonist, methamphetamines combined with a dopamine antagonist (amisulpride) and a placebo and found that methamphetamine attenuated the amount of activity correlating with the encoding of incentive values, or RPE, in the limbic striatum, and attenuated neural activity in the ventromedial prefrontal cortex (vmPFC) correlating with the encoding of incentive value. Pretreatment with amisulpride did not influence the effects of methamphetamines in the striatum or in the vmPFC, suggesting that, in

this study, effects may have also been driven by something other than D_2 dopamine receptors such as norepinephrine or D_1 dopamine receptors. Jocham et al. (2011) looked at the effects of amisulpride on a very similar decision-making task and found that a low dose of amisulpride increased the amount of activity in the striatum, correlating with RPEs, as well as enhancing neural activity in the vmPFC which was correlating with tracking learned value. Obviously, drug pharmacodynamics can vary with dose, though this differs between compounds and individuals. Unfortunately, the specifics of these interactions within the brain are commonly not well circumscribed. In the study by Jocham and colleagues the dose of amisulpride was lower than the dose usually administered in clinical settings, and there are data to support it having greater effects on presynaptic dopaminergic receptors at this dose (Green, 2002). Additionally, even animal studies have shown that low does dopamine antagonists can potentiate conditioned reinforcement opposite to larger doses (Smith et al., 1997) suggesting that this low dose of amisulpride may have acted on behaviour and neural activity in the opposite direction as if a larger dose had been administered. Together these studies show that dopaminergic manipulation has an effect on neural activity during decision-making, but the direction of this effect sometimes shows enhanced and other times shows attenuated activation. While a vast amount of animal literature suggests that dopamine agonists have a reinforcing effect on reward related learning, while dopamine antagonists impair reward related learning (Wise, 2004), the contradicting results in humans shows that a lot of work still needs to be done to explore dopamine perturbation in humans.

Additionally, most of these studies used only simple decision-making tasks. This study proposes to expand on these previous studies by incorporating social cues to standard

utilitarian decision-making factors while exploring the effects of dopaminergic perturbation on neural activity. Previous studies have already shown that incorporating social cues into a simple associative learning decision-making task can affect how participants make decisions by biasing their choices toward picking a happy face even when the evidence for reward supports choosing an angry face (Averbeck and Duchaine, 2009; Evans et al., 2011a; Furl et al., 2012). This study incorporated another element by also incorporating dopaminergic manipulation while undergoing fMRI during the same value-based decision-making task using facial expressions to explore social bias in decision-making during an associative learning task. Additionally, the task explored in this study incorporated a choice condition between two neutral faces in order to investigate non-socially salient task effects.

In light of current research, I hypothesise that:

1. Healthy controls will show the same bias as previously shown toward choosing the happy face in lieu of an angry face when given a placebo (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2011b; Furl et al., 2012) but that when given ropinirole and amisulpride, healthy controls will learn better reward contingency associations with the faces and learn to pick the more highly rewarding face regardless of social salience such that bias toward the happy face will be attenuated in both drug conditions.

2. On account of its shared pharmacology with L-DOPA, it is hypothesised that when deciding which face is more likely to be rewarded, dopaminergic perturbation by ropinirole, relative to placebo administration, will increase neural activity in regions along the mesolimbic dopamine pathway, particularly in regions subserving reward learning (such as the ACC) and emotion (such as the amygdala). By contrast, using a

higher dose of amisulpride, than previously explored with fMRI, will attenuate neural activity in these regions. Furthermore, these effects will be greater when making decisions between two emotionally valenced faces on account of their enhanced social salience compared with neutral faces. In addition, the change in neural activity in these regions will correlate with the degree of change in bias.

3. As previously demonstrated by Pessiglione et al. (2006), RPE will be modulated by dopamine perturbation such that ropinirole administration will act to increase neural activity in dopamine rich reward areas (such as the striatum, and specifically the ventral striatum), relative to placebo administration and amisulpride administration will act to attenuate neural activity in these regions relative to placebo administration when processing both emotionally valenced faces as well as neutral faces.

3.2 METHODS

3.2.1 PARTICIPANTS

Twenty seven healthy controls (22 males) were recruited for this study. Of these twenty-seven, seven participants did not complete all three scanning sessions leaving a final sample of 20 healthy controls (17 males). Intelligence quotient (IQ) was measured in all participants using the two-item Wechsler Abbreviated Scale of Intelligence (WASI) consisting of the vocabulary and matrix reasoning subtests (Wechsler 1999). Demographic information can be found below in Table 3.1. All participants signed informed consent and were compensated for their participation in the study. Ethical approval was obtained from the Central London Research and Ethics Committee 3. Further details of recruitment and inclusion and exclusion criteria can be found in Chapter 2 (page 35).

TABLE 3.1 - Demographics for healthy participants

	Healthy Participants (N=20) (mean (SD))
Age (years)	36.25 (9.41)
WASI IQ	107.30 (14.42)
Parental Occupation (NS-SeC)	2.35 (1.60)
Gender	18M, 2F

IQ = Intelligence quotient; M = Male; F = Female.
WASI = Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999)
NS - SeC = National Statistics Socio-economic Classification (Rose, 2001)

3.2.2 TASK

The task used was a forced-choice, stochastically rewarded decision-making task incorporating faces of varying social valence. In each trial two faces were presented to the left and the right of the screen. Pairs consisted of either: a happy face and an angry face of the same identity, or of two neutral faces of differing identities. Each visit consisted of two scanning sessions comprised of four counterbalanced blocks of 30 trials each (Figure 2.5, page 47). Pairs of emotionally valenced stimuli (i.e. happy and angry faces) were alternated with pairs of neutrally valenced stimuli (i.e. neutral faces). Within each emotionally valenced block, the identities of each face were kept consistent but the order of presentation of each identity was counterbalanced across sessions. Each block consisted of 30 trials with the presentation of each face counterbalanced across the left and right sides. Probability estimates were assigned to the faces at the beginning of each trial such that on 60% of the trials one face would win and 40% of trials the other face would win. The probability distribution of each face winning was counterbalanced across blocks such that the angry face won more in half of the blocks and the happy face won more in the other half, and that identity one won more over identity two for half of the blocks and vice versa for both the emotionally valenced and neutral faces. The order of these wins was counterbalanced

across the participants and visits. In each trial, participants were instructed to pick the face which, at that time, they believed was the most likely to win. They were told that after making this decision they would be told whether or not they had won where a win would show that they had won 10 pence along with their current winnings total and a loss was associated with no change in winnings and only the message "You lose." The presentation of stimuli is shown below in Figure 3.2. Further details, including the task instructions, can be found in Chapter 2 (page 44).

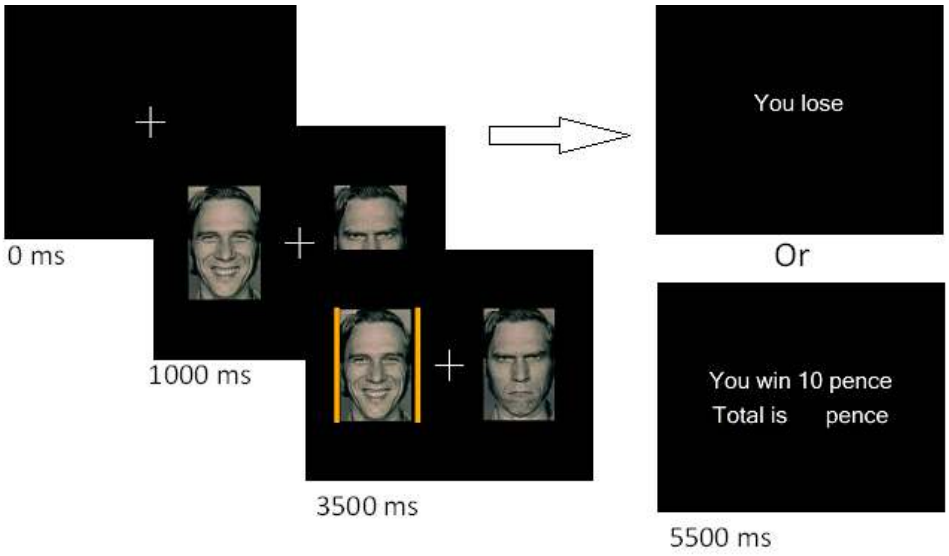

FIGURE 3.2 - Presentation of stimuli in the scanner in each trial

3.2.3 PHARMACOLOGICAL PROBES

Healthy controls were administered a dopamine agonist (Ropinirole (0.25mg)), dopamine antagonist (Amisulpride (400 mg)) or a Placebo consisting of ascorbic acid in a double-blind crossover design. Drug order was counterbalanced across days to balance the order in which participants received the drugs such that: on the first day 6 received placebo, 7 received amisulpride and 7 received ropinirole; on the second day 8 received placebo, 7 received amisulpride and 5 received ropinirole; on the third day 6 received placebo, 6 received amisulpride and 8 received ropinirole. All drug

conditions were counterbalanced so that each drug was administered at approximately equal amount of times across each testing day. All drugs were encapsulated and packaged by the South London and Maudsley (SLaM) pharmacy and were administered on the same day. Each drug was administered at a time to maximise its concentration in the plasma levels (T_{max}) at the time of the scan such that the first administration was timed four hours before the scan (to coincide with the T_{max} of amisulpride) and the second administration was timed two hours before the scan (to coincide with the T_{max} of ropinirole). A placebo was administered at each time slot where a drug was not administered. Scans were scheduled a minimum of one week apart to allow for an adequate washout period of each drug administered. Further details of each of the drugs used can be found in Chapter 2 (page 39).

3.2.4 FMRI DATA ACQUISITION

Functional magnetic resonance imaging (fMRI) data were acquired on a Discovery MR750 3T scanner at the Centre for Neuroimaging Sciences, London (T2* weighted gradient-echo echo-planar images (EPIs), repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, flip angle = 75°, 64 x 64 matrix, 24cm field of view). A 12-phase head coil array was used over the whole head for RF transmission and reception. Each whole-brain image contained 38 3-mm axial slices separated by a distance of 0.3 mm with in-plane isotropic voxel resolution of 3.75 x 3.75 mm. For each block, 430 scans were acquired and two sessions were recorded for each participant.

Before the experimental portion of the experiment, a T1-weighted structural scan using a fast-spoiled gradient-echo pulse sequence (TR = 9.356 ms, TE = 3.828 ms, flip angle = 12°, time to inversion = 450 ms) was acquired for reference purposes. The first four volumes were discarded to allow for transient effects.

Participants made their responses using a two buttons on a three button-box with their index and middle fingers of their right hand. Head movement was minimised using headphones and additional padding around the head and ears as well as around the arms and legs.

3.2.5 ANALYSIS

All data were preprocessed and analysed using Statistical Parametric Mapping 12 (SPM12) (Wellcome Department of Imaging Neuroscience, London, UK. www.fil.ion.ucl.ac.uk/spm) and MATLAB R2014a (MathWorks Inc. Sherbon, MA, USA). Further details of these steps can be found in Chapter 2 (page 53).

A general linear model (GLM) was constructed in SPM12 to analyse the images with each event modelled as a delta (stick) function. Each block, consisting of 30 trials, was modelled independently and was defined as being either a block using emotionally valenced faces (e.g. happy and angry faces) or neutral faces (e.g. two faces of different identities). Events of interest within each block included the presentation of the faces, a decision-making regressor indicating when the decision was made for which face the subject believed would be rewarded (determined by a button press), and the feedback presentation within each trial. Also modelled were regressors to represent the motion parameters as well as parametric modulators on the decision-making regressor for the probability of each face chosen being associated with a win and feedback regressors. The probability that the face they picked would win was calculated using an ideal observer. The calculations used to determine this probability are outlined in depth in Chapter 2 (page 47). The feedback regressor, associated with when they were given feedback about whether or not the face they had chosen was associated with a reward, was parametrically modulated by the reward prediction error (RPE)

determined by subtracting the actual reward (i.e. 1 for a win and 0 for a loss) from the predicted probability that the chosen face would win as detailed in Chapter 2 (page 49). Each regressor, except for the motion parameters, was convolved with a canonical hemodynamic response function and its temporal derivative. Missed trials were not modelled as events. Blocks where subjects failed to respond for greater than 50% of the trials were excluded from analysis as they were deemed to be insufficiently attending to the task. Furthermore, without feedback from all trials, it would have been more difficult for subjects to accurately assess which face was winning more often throughout the block. These excluded blocks accounted for 2 blocks across 2 subjects, both in the amisulpride condition (both blocks were when making decisions between two neutral faces).

Performance estimates were calculated across all trials by comparing the face the subject picked to the face the ideal observer assigned the highest probability of winning. In the case that both faces had equal probability of winning (i.e. at 50% probability) either face picked was deemed optimal. Overall performance estimates were calculated across all trials as the number of times the participant picked the face deemed optimal over the number of valid trials (i.e. 30 – any misses). These estimates were then averaged across all blocks which were not excluded to get an overall performance estimate for all blocks using emotionally valenced and neutral faces.

To assess how facial expression biased decision-making, all trials were separated into when participants agreed with the ideal observer and when they disagreed with the ideal observer for each facial valence as well as for the two neutral face identities. A 2x2 contingency table was calculated for each block type (i.e. emotionally valenced and neutral) representing choices by the ideal observer and choices by the participant.

When the probability for each face winning was ambiguous (i.e. equal probabilities for both faces), the contingency count for each face was increased by 0.5. Using this table it was possible to calculate the conditional probability of each participant choosing the happy face when they should have chosen the angry face given the current evidence for the angry face *p*(happy|angry) as well as when they chose the angry face when they should have chosen the happy face given the current evidence for the happy face *p*(angry|happy). The difference between these two measures was calculated to represent the degree of bias toward picking the happy face (*p*(happy|angry) – *p*(angry|happy)). This measure indicates how often participants ignore the evidence that has accumulated for the negatively valenced face and chose the positively valenced face compared to how often they ignored evidence that had accrued for the positively valenced face and chose the negatively valenced face. This bias distribution was examined across all participants and entered into a one sample t-test to see if it significantly differed from 0. It is important to note these conditional probabilities were calculated separately to the probability that each face would win. A more comprehensive overview with equations is provided in Chapter 2 (page 49). This process has been replicated in multiple studies to represent the degree of bias (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2010; Evans et al., 2011b; Furl et al., 2012).

The main focus of this study was to look at how decision-making and RPE affected neural activity so contrasts were looked at representing neural activity when a button was pressed to indicate which face the participant had chosen on a given trial, here after referred to as the decision-making condition as well as contrasts representing neural activity correlating with RPE given by the parametric modulator on reward

feedback. Second-level contrasts between drug conditions were assessed using paired sample t-tests and overall effects of task were assessed using a one sample t-test in the placebo condition. Within each drug comparison (i.e. amisulpride versus placebo and ropinirole versus placebo), the main effect of task was analysed looking at by combining the blocks for emotionally valenced and neutral faces. Then contrasts were also created for blocks looking at only decision-making between the emotionally valenced faces to assess differences in decision-making with emotionally salient stimuli as well as within only the blocks looking at decision-making between neutral faces to assess differences in decision-making between general social stimuli with no emotional salience. Interaction effects between the emotion and drug were also analysed to see if there was any interaction between the emotionally valenced face condition and the neutral face condition and the drug they were administered.

To look at interaction effects between drugs and emotion an overall examination of blocks looking at the effects of drug (i.e. ropinirole versus placebo and amisulpride versus placebo) and emotion (i.e. emotionally valenced versus neutral faces) were entered into 2x2 full factorial in SPM12 with drug and emotion as conditions.

Contrasts were whole brain cluster-level family wise error (FWE) corrected at $p<.05$ with a height threshold of $p < .005$, uncorrected, and an extent threshold of 100 contiguous voxels. Voxels which survived peak level FWE correction at $p<.05$ are also reported. When looking at the main effect of task and emotion in the placebo condition, cluster level results are reported at a more stringent height threshold of $p < .001$. Reported voxels coordinates were converted from Montreal Neurological Institute (mni) coordinates into Talairach coordinates using the function icbm_spm2tal (Laird et al., 2010; Lancaster et al., 2007a) and were entered into Talairach Daemon to

confirm their location in gray matter (Lancaster et al., 1997; Lancaster et al., 2000). Questionable results were further visualised by entering the original mni coordinates into xjview (http://www.alivelearn.net/xjview). Results are reported as their original mni coordinates as output by SPM12. If more than one voxel was found to be significant within a region without *a priori* interest, only the peak voxel is reported. Additionally, the contrast estimates from each image were analysed at the peak voxels to determine the direction of change between each condition analysed as significant decreases under one condition could still appear as increases in another condition even if no change in neural activity was present.

Region of interest analyses were also carried out within regions with an *a priori* interest to our study using small volume correction (SVC) within SPM12. Volumes of interest were defined using WFU PickAtlas Tool (Maldjian et al., 2003) for the amygdala and striatum and the ventral striatum was taken from Mawlawi et al. (2001). Only voxels which survived FWE correction at a peak level of p <.05 are reported.

3.3 RESULTS

3.3.1 BEHAVIOURAL ANALYSIS

3.3.1.1 PERFORMANCE

On average, all subjects were able to perform the task at above chance levels (mean performance estimates across all trial types 0.71 ± 0.15, see Table 3.2 for estimates for each trial type). To assess performance, the face picked by the subject on each trial was compared to an ideal observer calculated based on the number of times a face won or would have won over the number of valid trials. Performance estimates were averaged separately across all neutral face trials and emotionally valenced face trials for each subject and are shown in Figure 3.3 and Figure 3.4.

TABLE 3.2 - Performance estimates across drug conditions referenced to an ideal observer in terms of percentage agreement

	Emotional faces	**Neutral faces**	**Difference from Chance (50%)**	
	mean (SD)	*mean (SD)*	*Emotional faces*	*Neutral faces*
Placebo	70.9% (15.7%)	68.9% (17.5%)	*p*>.05	*p*>.05
Amisulpride	71.1% (15.1%)	67.7% (16.4%)	*p*>.05	*p*>.05
Ropinirole	72.3% (13.5%)	67.3% (12.4%)	*p*>.05	*p*>.05
Total	71.4% (14.6%)	67.9% (15.3%)		

SD = Standard deviation

Performance is measured in terms of percentage accordance to an ideal observer. This is looked at separately across all blocks using emotionally valenced faces and neutral faces and t value were calculated to show significant difference from chance

FIGURE 3.3 - Performance estimates compared to an ideal observer across drug conditions in healthy participants when deciding between emotionally valenced faces where performance is compared to an ideal observer on a trial by trial basis. Each cross represents the performance of a single individual and the line represents the mean across all subjects.

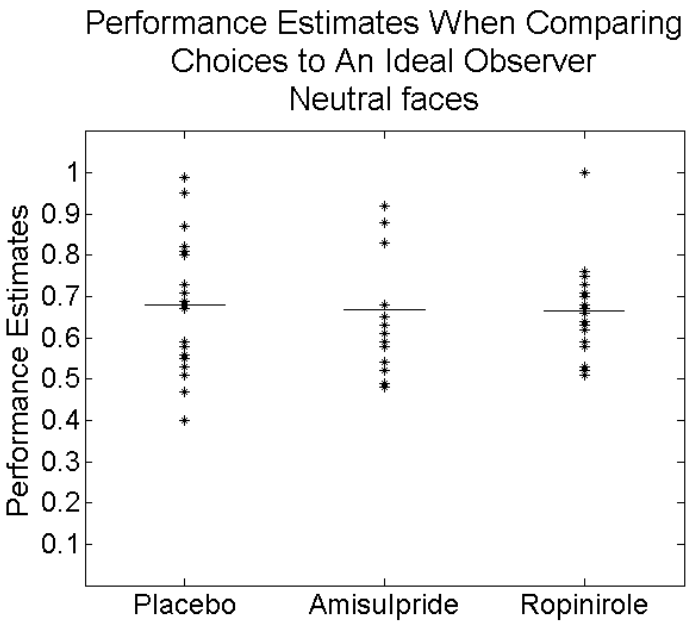

FIGURE 3.4 - Performance estimates compared to an ideal observer across drug conditions in healthy participants when deciding between neutral faces where performance is compared to an ideal observer on a trial by trial basis. Each cross represents the performance of a single individual and the line represents the mean across all subjects

3.3.1.2 BIAS MEASURES

The distribution of bias toward picking the happy face was found to be significantly different from 0 only after receiving a placebo and at a trend level after being administered amisulpride. No bias was observed after subjects were administered ropinirole however, this attenuation of bias was not significantly different from after receiving a placebo (t(19) = 0.828, p = 0.418). No significant biases were observed in the neutral condition, but, after being administered placebo, healthy controls show a trend level bias toward picking one of the neutral faces.

TABLE 3.3 - Bias estimates toward a happy face and a neutral identity and their significance levels

	Emotional	**Neutral**	**Bias significance**	
	mean (SD)	*mean (SD)*	*Emotional faces*	*Neutral faces*
Placebo	0.08 (0.11)	-0.07 (0.18)	t(19) = 3.11, p=0.006*	t(19) = 1.82, p=0.085†
Amisulpride	0.06 (0.14)	0.05 (0.23)	t(19) = 1.94, p=0.068†	t(19) = 0.867, p=0.397
Ropinirole	0.07 (0.19)	-0.02 (0.16)	t(19) = 1.59, p=0.128	t(19) = 0.60, p=0.556

* significant at p<0.05, † trend level significance at p<0.1, SD = Standard deviation

Bias estimates are estimated as the degree of bias toward picking one of the faces when the ideal observer supports the other face as the better option using a contingency table described on page 49. Bias significance was calculated as the difference from 0

3.3.2 FMRI ANALYSIS

3.3.2.1 DECISION-MAKING

Neural activity was analysed when each of the participants made a button press to indicate their decision about which face they believed would be rewarded.

3.3.2.1.1 MAIN EFFECT OF DECISION-MAKING (PLACEBO)

Neural activity in healthy participants after taking a placebo during decision-making across both emotionally valenced and neutral face conditions affected a range of regions throughout the brain ranging from the medial frontal gyrus to the cerebellum. The list of regions within each decision-making condition for this task can be found in Table 3.4 and is pictured in Figure 3.5.

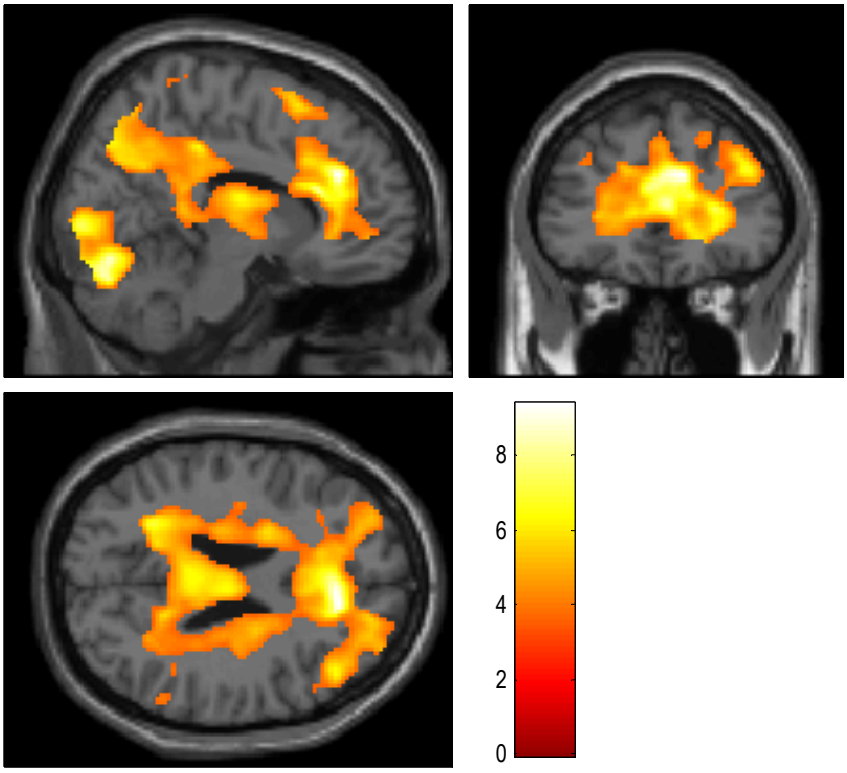

FIGURE 3.5 - Neural activity for decision-making across both emotionally valenced and neutral faces after taking a placebo.This shows the main effect of decision-making within healthy participants after taking a placebo. This image is shown at an uncorrected height threshold of $p < 0.001$ with an extent threshold of 100 and only clusters surviving FWE cluster-level correction of $p < 0.05$

3.3.2.1.2 DIFFERENCE IN NEURAL ACTIVITY BETWEEN EMOTIONALLY VALENCED FACES AND NEUTRAL FACES (PLACEBO)

Neural activity in healthy participants who have taken a placebo when deciding between neutral faces was greater than when deciding between emotionally valenced faces within the right cingulate gyrus extending into the bilateral anterior cingulate, cuneus, the left middle occipital lobe, the right dorsolateral prefrontal cortex (dlPFC) as well as the right cerebellum extending through the tentorium into the fusiform and parahippocampal gyrus (Figure 3.6 and Table 3.4).

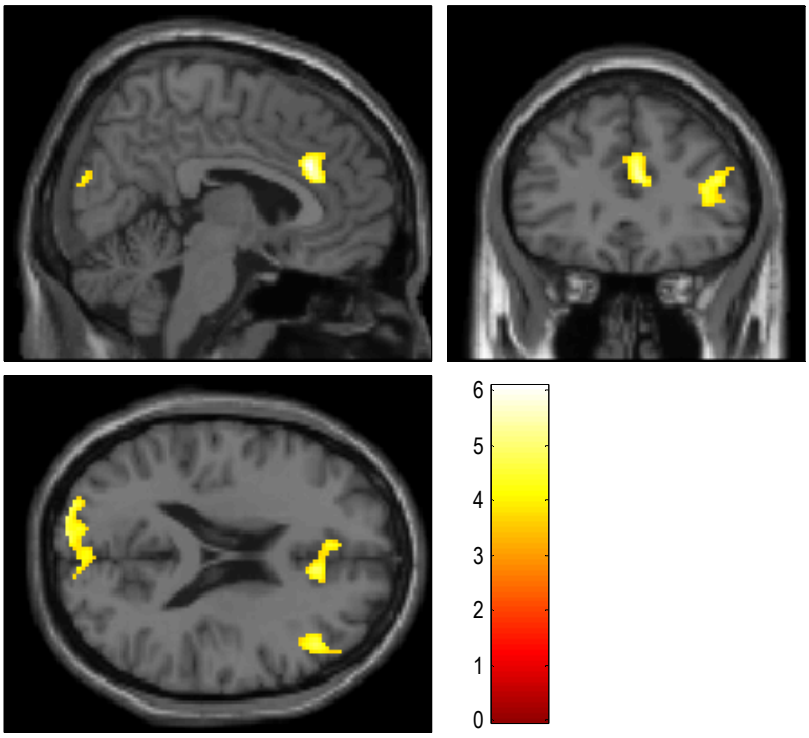

FIGURE 3.6 - The difference in neural activity between deciding between neutral faces and emotionally valenced faces.Showing greater neural activity in the right cingulate gyrus extending into the bilateral anterior cingulate, cuneus, the left middle occipital lobe, the right dorsolateral prefrontal cortex (dlPFC) as well as the right cerebellum extending through the tentorium into the fusiform and parahippocampal gyrus for decision-making between neutral faces over emotionally valenced faces. This image is shown at an uncorrected height threshold of $p < 0.001$ with an extent threshold of 100 and only clusters surviving FWE cluster-level correction of $p < 0.05$.

TABLE 3.4 - Neural activity during decision-making after taking a placebo

Condition	Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k
Decision (Emotional and Neutral faces)										
	R	Medial Frontal Gyrus*	9	11	36	26	9.39	<.001	<.001	42733
	L	Superior Frontal Gyrus*	6	1	20	56	8.55	<.001	<.001	42733
	R	Cingulate Gyrus*	32	7	34	26	9.22	<.001	<.001	42733
	L	Cingulate Gyrus*	32	-1	34	22	8.89	<.001	<.001	42733
	R	Anterior Cingulate*	24	3	38	12	8.54	<.001	<.001	42733
	L	Precentral Gyrus*	6	-31	-10	64	8.96	<.001	<.001	42733
	R	Precentral Gyrus*	9	43	30	34	8.23	<.001	<.001	42733
	L	Inferior Parietal Lobule*	40	-43	-36	60	8.84	<.001	<.001	42733
	R	Inferior Parietal Lobule*	40	47	-44	54	6.63	<.001	<.001	42734
	L	Thalamus (LPN)*		-19	-18	16	8.48	<.001	<.001	42733
	R	Thalamus (VLN)*		19	-12	16	7.16	<.001	<.001	42733
	L	Lingual Gyrus*	18	-7	-92	-2	8.35	<.001	<.001	42733
	R	Lingual Gyrus*		7	-72	-12	8.43	<.001	<.001	42733
	R	Supramarginal Gyrus (TPJ)*	40	53	-42	38	7.83	<.001	<.001	42733
	L	Supramarginal Gyrus (TPJ)*	40	-45	-48	38	6.61	<.001	<.001	42733
	R	Middle Temporal Gyrus*	20	57	-44	-12	7.45	<.001	<.001	42733
	L	Middle Temporal Gyrus*	39	-27	-54	26	6.89	<.001	<.001	42733
	R	Lateral Globus Pallidus*		29	-10	-6	7.06	<.001	<.001	42733
	L	Putamen*		-27	-24	0	6.90	<.001	<.001	42733
	R	Precuneus*	7	17	-68	54	6.87	<.001	<.001	42733
	R	Fusiform Gyrus		27	-66	-14	4.68	<.001	<.001	42734
	L	Cerebellum (Pyramis)*		-19	-80	-30	8.67	<.001	<.001	42733

Condition	Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k
	R	Cerebellum (Declive)*		13	-76	-18	8.64	<.001	<.001	42733
Decision (Emotional and Neutral faces deactivation)										
	R	Postcentral Gyrus	3	57	-10	44	6.01	<.001	<.001	923
	R	Precentral Gyrus	6	61	2	36	5.9	<.001	<.001	923
	R	Postcentral Gyrus	40	41	-30	54	5.42	<.001	<.001	923
	R	Postcentral Gyrus	2	37	-24	46	5.01	<.001	<.001	923
	R	Postcentral Gyrus	3	49	-14	56	4.91	<.001	<.001	923
Decision (Neutral faces > Emotional faces)										
	R	Cingulate Gyrus	32	5	30	28	6.07	<.001	0.021	259
	L	Anterior Cingulate	32	-5	40	18	4.73	<.001	0.021	259
	R	Anterior Cingulate	32	11	40	14	4.09	<.001	0.021	259
	L	Cuneus	18	1	-82	24	5.25	<.001	0.013	290
	L	Cuneus	17	-13	-82	16	4.63	<.001	0.013	290
	L	Cuneus	18	-13	-88	20	4.35	<.001	0.013	290
	R	Cuneus	18	7	-88	20	4.11	<.001	0.013	290
	R	Cuneus	17	11	-92	16	3.82	0.001	0.013	290
	L	Middle Occipital Gyrus	18	-9	-94	18	4.83	<.001	0.013	290
	L	Middle Occipital Gyrus	18	-19	-94	20	4.81	<.001	0.013	290
	L	Middle Occipital Gyrus	18	-25	-90	20	4.72	<.001	0.013	290
	R	Middle Frontal Gyrus (dlPFC)	9	45	32	20	4.72	<.001	0.038	222
	R	Middle Frontal Gyrus (dlPFC)	9	53	34	26	3.95	<.001	0.038	222
	R	Fusiform Gyrus/Parahippocampal Gyrus	37	27	-46	-14	3.59	0.001	0.021	261
	R	Cerebellum (Culmen)		25	-44	-24	4.51	<.001	0.021	261
	R	Cerebellum (Declive)		41	-64	-24	4.21	<.001	0.021	261

Condition	Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k
	R	Cerebellum (Uvula)		37	-72	-24	4.03	<.001	0.021	261

Corresponding coordinates for each brain region listed represent the peak voxels for each corresponding region within each significant cluster. All areas reported were found to be significant at a family wise error (FWE) cluster level corrected threshold of <.05 after running a whole brain analysis at an uncorrected threshold of p<.001. *regions which also survive p < .05 FWE peak level correction; k = cluster size; BA = Brodmann's Area

3.3.2.1.3 DECISION-MAKING IN PLACEBO VERSUS ROPINIROLE

3.3.2.1.3.1 MAIN EFFECT OF DECISION-MAKING ACROSS EMOTIONALLY VALENCED AND NEUTRAL FACES (ROPINIROLE VERSUS PLACEBO)

When deciding which face is most likely to be rewarded between two emotionally valenced faces and two neutral faces, healthy controls show no differences in neural activity between when they have taken a placebo versus after they have taken ropinirole.

3.3.2.1.3.2 DECISION-MAKING BETWEEN EMOTIONALLY VALENCED FACES (ROPINIROLE VERSUS PLACEBO)

When deciding which of two emotionally valenced faces was most likely to be rewarded, healthy controls showed greater neural activity after being administered ropinirole versus a placebo in the left dorsal anterior cingulate (dACC) extending into the bilateral cingulate gyrus and left dorsomedial prefrontal cortex (dmPFC) (Figure 3.7 and Table 3.5).

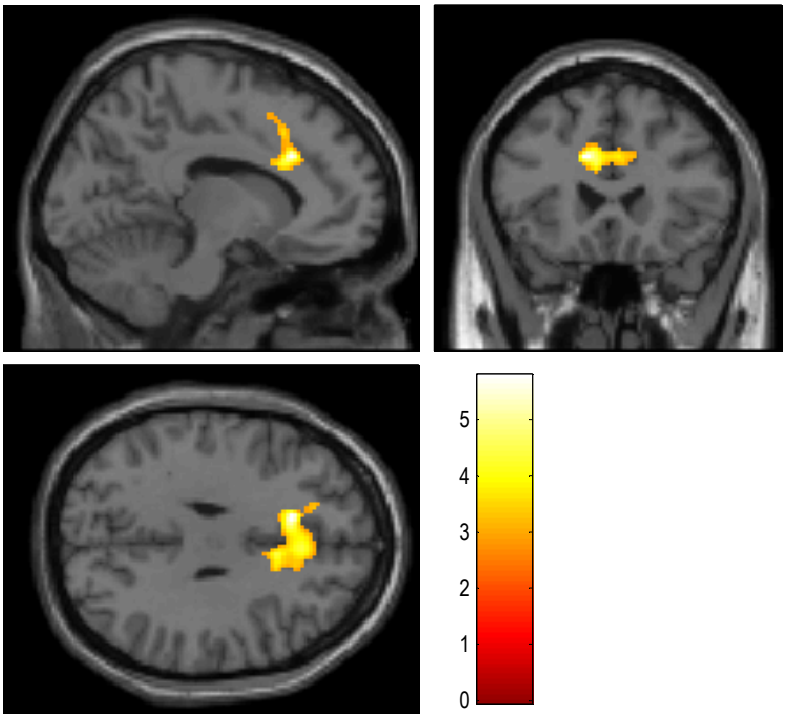

FIGURE 3.7 - Neural activity after being administered ropinirole over a placebo when deciding between two emotionally valenced facesThis image is shown at an uncorrected height threshold of $p < 0.005$ with an extent threshold of 100 and only clusters surviving FWE cluster-level correction of $p < 0.05$

Furthermore, as the amygdala is an area often implicated in emotional processing (Adolphs, 2010; Dyck et al., 2011), a region of interest (ROI) analysis using small volume correction (SVC) was performed within a mask for the right and left amygdala. Neural activity was significantly attenuated after ropinirole administration over placebo administration in the right amygdala (peak, x = 33, y = 0, z = -28), t(19) = 4.02, p = 0.014, k = 32, with p representing the significance at FWE peak level correction, when looking at neural activity during decision-making between two emotionally valenced (Figure 3.8 and Table 3.5).

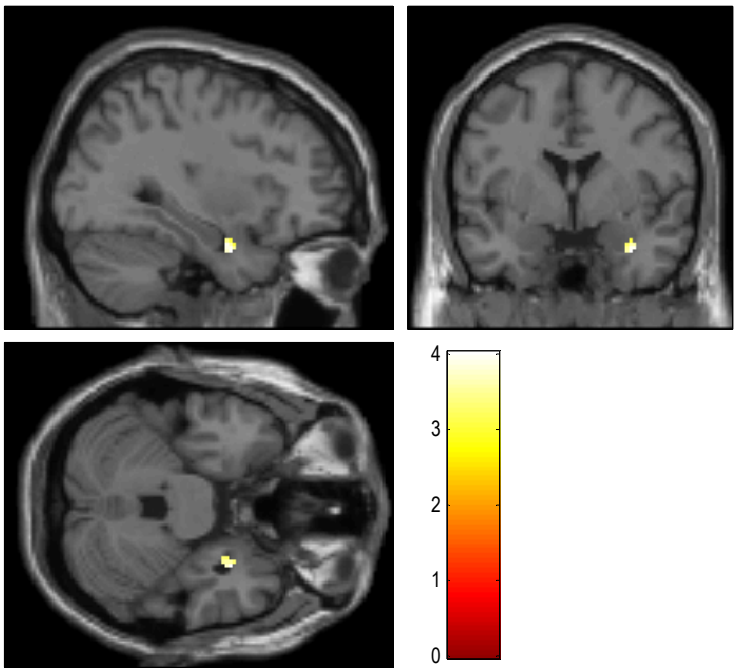

FIGURE 3.8 - Neural activity after being administered ropinirole over a placebo when deciding between two emotionally valenced facesThis image is shown at an uncorrected height threshold of $p < 0.005$ with all peaks surviving FWE cluster-level correction of $p < 0.05$

As bias was also attenuated after the administration of ropinirole, mean values from within the cluster found in the dmPFC and dACC were extracted using spm_summarise() to see if attenuation was driven by the changes in neural activity within these regions. Although the change in bias measures did not correlate with the mean change in neural activity within this region between ropinirole and placebo

administration for each participant (r = 0.34, p = 0.133 (two-tailed)). However, the bias measurements after placebo administration were strongly negatively correlated with the change in neural activity between the two drug conditions (r = -0.71, p < 0.001), suggesting that initial bias measures may have influenced how much each participant was influenced by ropinirole in this region. Furthermore, bias measures after receiving placebo also correlated with neural activity after receiving a placebo in this region (r = 0.45, p = 0.047) suggesting that the mean neural activity was increased across all subjects regardless of their original bias measures after being administered ropinirole compared to a placebo and that those with stronger biases exhibited generally higher levels of neural activity in this region after placebo administration.

3.3.2.1.3.3 DECISION-MAKING BETWEEN NEUTRAL FACES (ROPINIROLE VERSUS PLACEBO)

When deciding which face is most likely to be rewarded between two neutral faces, healthy controls show no differences in neural activity between when they have taken a placebo versus after they have taken ropinirole.

3.3.2.1.3.4 INTERACTION EFFECTS FOR DECISION-MAKING BETWEEN EMOTIONALLY VALENCED AND NEUTRAL FACES (ROPINIROLE VERSUS PLACEBO)

When looking for any interaction effects between decision-making in the emotionally valenced faces compared to the neutral faces after receiving placebo and ropinirole, no significant differences were found in neural activity at a whole brain level. However after a region of interest (ROI) analysis using small volume correction (SVC) was performed within a mask for the left and right amygdala. There was a significant interaction effect in the right amygdala (x = 33, y = 2, z = -26), t(76) = 3.63, p = 0.008, k = 26, and a trend toward significance in the left amygdala (x = -27, y = 2, z = -24), t(76) = 2.66, p = 0.082, k = 1, with p representing the significance at FWE peak level correction, when comparing the interaction between drug (placebo versus ropinirole)

and emotion (emotionally valenced versus neutral faces) (Figure 3.9 and Table 3.5). This effect was found to be driven by a stronger decrease in neural activity within the amygdala after being administered ropinirole than placebo (Figure 3.10) and was mainly driven by a difference in neural activity when deciding between emotionally valenced faces as demonstrated on page 79.

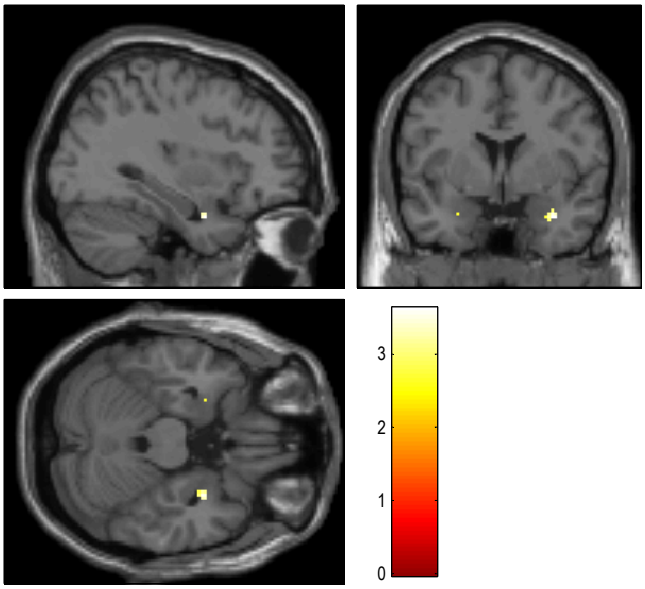

FIGURE 3.9 - Neural activity for interaction effects between drug conditions (placebo versus ropinirole) and emotion (emotionally valenced versus neutral faces) This image is shown at an uncorrected height threshold of $p < 0.005$ with all peaks surviving FWE cluster-level correction of $p < 0.05$

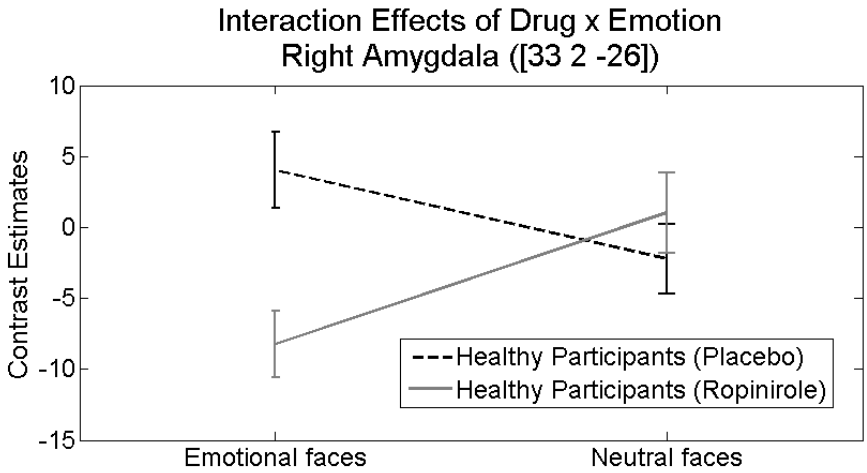

FIGURE 3.10 - Contrast estimates within the right amygdala showing interaction effects for drug (placebo versus ropinirole) by emotion (emotionally valenced versus neutral faces). This image shows that there is a significant attenuation of neural activity in the amygdala by ropinirole when processing emotional faces which is slightly greater than activity compared to the placebo condition when deciding between two neutral faces

TABLE 3.5 – Difference in neural activity for decision-making after taking a placebo versus ropinirole

Drug comparison	Condition	Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
Ropinirole > Placebo	Decision (Emotional faces)	L	Cingulate Gyrus	32	-11	24	30	5.80	<.001	0.004	887	1.88
		R	Cingulate Gyrus	32	5	32	24	5.14	<.001	0.004	887	1.67
		R	Cingulate Gyrus	24	7	16	28	4.54	<.001	0.004	887	1.47
		L	Anterior Cingulate	32	-3	36	20	3.76	0.001	0.004	887	1.22
		L	Anterior Cingulate	33	1	16	20	3.67	0.001	0.004	887	1.19
		L	Medial Frontal Gyrus (dmPFC)	32	-9	20	42	3.80	0.001	0.004	887	1.23
		L	Medial Frontal Gyrus (dmPFC)	6	-19	36	32	3.38	0.002	0.004	887	1.10
		L	Medial Frontal Gyrus	6	-13	14	50	3.11	0.003	0.004	887	1.01
Placebo > Ropinirole	Emotional faces	R	Amygdala[a]		33	0	-28	4.02	<.001	0.014*	32	1.30
		R	Amygdala[a]		33	-2	-24	3.88	0.001	0.018*	32	1.26
		R	Amygdala[a]		29	-4	-20	3.47	0.001	0.038*	32	1.13
Drug (Ropinirole x Placebo) x Emotion (Emotionally valenced x Neutral faces)		R	Amygdala[a]		33	2	-26	3.63	<.001	0.008*	26	1.18
		L	Amygdala[a]		-27	2	-24	2.66	0.005	0.082*	1	0.86

Corresponding coordinates for each brain region listed represent the peak voxels for each corresponding region within each significant cluster. All areas reported were found to be significant at a family wise error cluster level corrected threshold of <.05 after running a whole brain analysis at an uncorrected threshold of p<.005. *values for peak level FWE correction using small volume correction [a]areas looked at using small volume correction; k = cluster size BA = Brodmann's Area
Effect size was calculated using Cohen's d

3.3.2.1.4 DECISION-MAKING IN PLACEBO VERSUS AMISULPRIDE

3.3.2.1.4.1 MAIN EFFECT OF DECISION-MAKING ACROSS EMOTIONALLY VALENCED AND NEUTRAL FACES (AMISULPRIDE VERSUS PLACEBO)

When deciding which face is most likely to be rewarded between two emotionally valenced faces and two neutral faces, healthy controls showed no differences in neural activity between when they have taken a placebo versus after they have taken amisulpride.

3.3.2.1.4.2 DECISION-MAKING BETWEEN EMOTIONALLY VALENCED FACES (AMISULPRIDE VERSUS PLACEBO)

When deciding which face is most likely to be rewarded between two emotionally valenced faces, healthy controls showed no differences in neural activity between when they have taken a placebo versus after they have taken amisulpride.

3.3.2.1.4.3 DECISION-MAKING BETWEEN NEUTRAL FACES (AMISULPRIDE VERSUS PLACEBO)

When deciding which face is most likely to be rewarded between two neutral faces, healthy controls showed greater neural activity in the bilateral cerebellum extending through the tentorium into the right parahippocampal gyrus, lingual gyrus and fusiform gyrus for placebo administration relative to amisulpride administration (Table 3.6 and FIGURE 3.11).

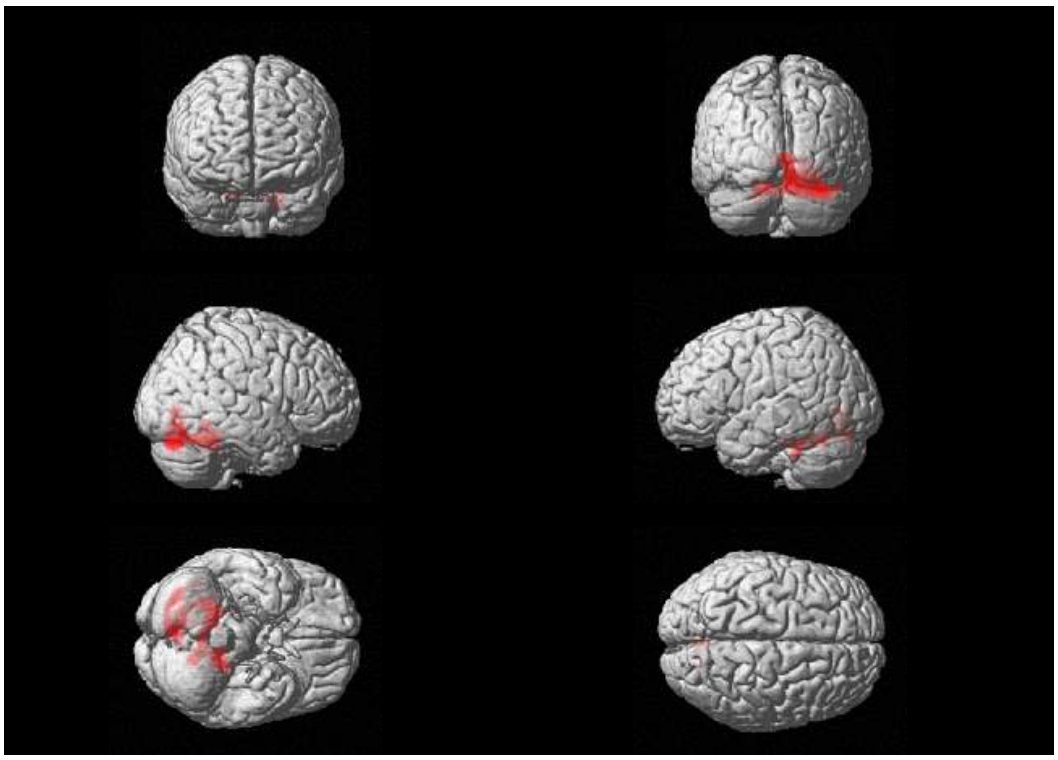

FIGURE 3.11 - Neural activity for placebo versus amisulpride when choosing between neutral faces showing attenuated neural activity in the bilateral cerebellum and through the tentorium into the right fusiform gyrus after amisulpride administration. This image is shown at an uncorrected height threshold of $p < 0.005$ with all peaks surviving FWE cluster-level correction of $p < 0.05$ and an extent threshold of k = 100.

3.3.2.1.4.4 INTERACTION EFFECTS FOR DECISION-MAKING BETWEEN EMOTIONALLY VALENCED AND NEUTRAL FACES (AMISULPRIDE VERSUS PLACEBO)

When looking for any interaction effects between decision-making for drug (amisulpride versus placebo) by emotion (emotionally valenced versus neutral faces), no significant differences were found in neural activity at a whole brain level. An ROI analysis using SVC was carried out in the left and right amygdala however, only a trend toward significance was found in the left amygdala at (x = -27, y = 2, z = -24), t(76) = 2.72, $p = 0.071$, k = 2, with p representing the significance at FWE peak level correction, when comparing the interaction between emotional and neutral stimuli between healthy controls who have taken a placebo and amisulpride (Table 3.6).

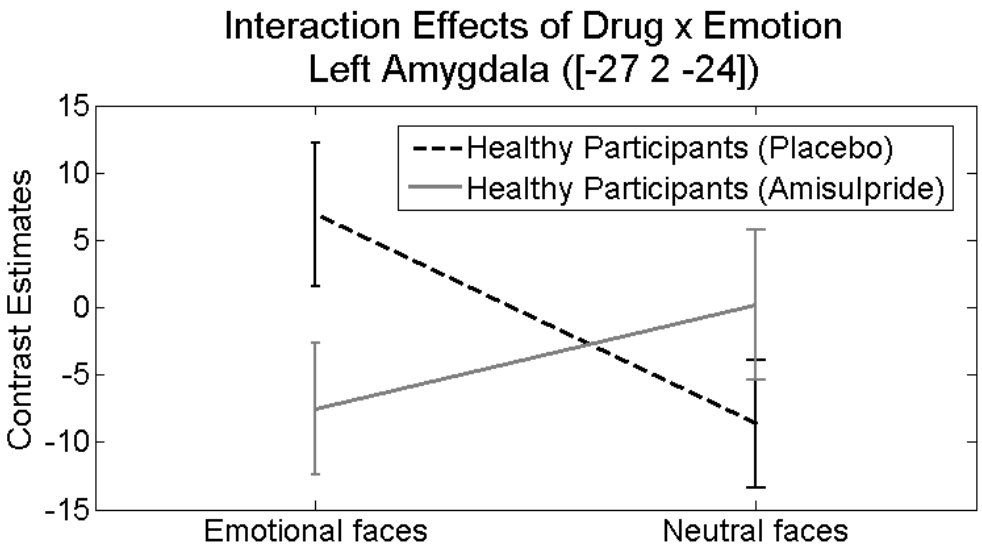

FIGURE 3.12 - Contrast estimates within the left amygdala showing interaction effects for (placebo versus amisulpride) by emotion (emotionally valenced versus neutral faces). This image shows that there is a trend toward a significant interaction effect of drug by emotion on neural activity in the amygdala for amisulpride when processing emotional faces which is slightly greater than activity compared to the placebo condition when deciding between two neutral faces

TABLE 3.6 - Difference in neural activity for placebo versus amisulpride administration during decision-making

Drug Comparison	Condition	Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
Placebo > Amisulpride	Decision (Neutral faces)	R	Parahippocampal Gyrus	37	29	-50	-12	3.85	0.001	<.001	1656	1.25
		R	Lingual Gyrus	18	5	-74	-4	3.86	0.001	<.001	1656	1.25
		R	Fusiform/Lingual Gyrus		21	-70	-12	3.43	0.001	<.001	1656	1.11
		R	Fusiform Gyrus	37	47	-58	-22	3.61	0.001	<.001	1656	1.17
		L	Cerebellum		-15	-44	-26	6.04	<.001	<.001	1656	1.96
		L	Cerebellum		-13	-60	-22	5.16	<.001	<.001	1656	1.67
		L	Cerebellum (Cerebellar Tonsil)		-19	-38	-36	4.10	<.001	<.001	1656	1.33
		L	Cerebellum (Culmen)		-21	-32	-26	3.58	0.001	<.001	1656	1.16
		R	Cerebellum (Culmen)		21	-46	-24	5.66	<.001	<.001	1656	1.84
		R	Cerebellum (Culmen)		3	-54	-24	3.77	0.001	<.001	1656	1.22
		R	Cerebellum (Pyramis)		31	-78	-28	4.43	<.001	<.001	1656	1.44
		R	Cerebellum (Pyramis)		11	-82	-24	3.56	0.001	<.001	1656	1.16
		R	Cerebellum (Uvula)		37	-72	-24	4.05	<.001	<.001	1656	1.31
		R	Cerebellum (Declive)		7	-80	-22	3.65	0.001	<.001	1656	1.18
		R	Cerebellum (Declive)		15	-68	-18	3.59	0.001	<.001	1656	1.16
		R	Cerebellum (Declive)		7	-70	-12	3.56	0.001	<.001	1656	1.16
Drug (Amisulpride x Placebo) x Emotion (Emotionally valenced x Neutral faces)		L	Amygdala[a]		-27	2	-24	2.72	0.004	.071[*]	2	0.88

Corresponding coordinates for each brain region listed for peak voxels for each corresponding region within each significant cluster. All areas reported were found to be significant at a family wise error cluster level corrected threshold of <.05 after running a whole brain analysis at an uncorrected threshold of p<.005; k = cluster size BA = Brodmann's Area
*values for peak level FWE correction using small volume correction; [a]areas looked at using small volume correction;
Effect size was calculated using Cohen's d

3.3.2.2 REWARD PREDICTION ERROR (RPE)

3.3.2.2.1 MAIN EFFECT OF RPE (PLACEBO)

Neural activity after being given a placebo correlating with RPE activated two significant clusters bilaterally in occipital cortex extending into the bilateral fusiform gyrus, left cuneus, right precuneus, and bilateral cerebellum (Figure 3.13 and Table 3.7).

As previous studies have shown RPE to correlate with neural activity in the striatum and ventral striatum (Jocham et al., 2011; Pessiglione et al., 2006), an ROI analysis using SVC was carried out in these regions however, no significant neural activity was found.

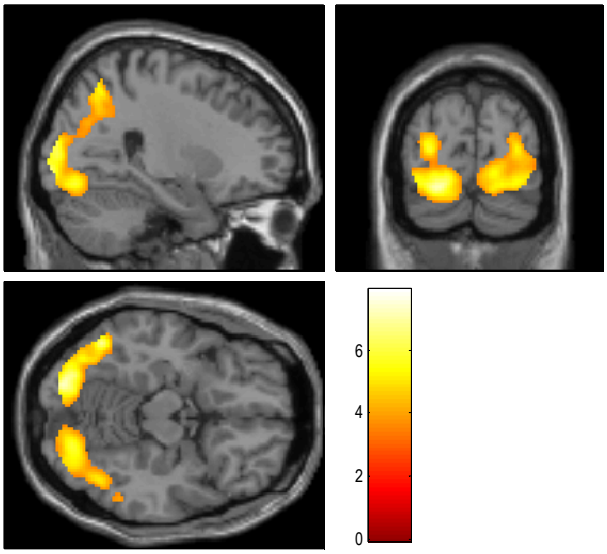

FIGURE 3.13 - Neural activity after receiving placebo correlating with RPE. showing increased neural activity in the bilateral occipital cortex extending through the tentorium into the fusiform gyrus, cerebellum, left cuneus and right precuneus. This image is shown at an uncorrected height threshold of $p < 0.001$ with an extent threshold of 100 showing only clusters surviving FWE cluster-level correction of $p < 0.05$

3.3.2.2.2 EFFECT OF EMOTION ON RPE (PLACEBO)

When looking at the differences in neural activity for RPE between when deciding between emotionally valenced faces versus neutral faces, healthy controls who have taken a placebo show no differences in neural activity even after SVC in the striatum and ventral striatum.

TABLE 3.7 - Neural activation correlating with RPE after receiving placebo

Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
RPE (Emotional and Neutral faces)										
L	Cuneus*	17	-13	-100	2	7.91	<.001	<.001	2604	2.57
L	Middle Occipital Gyrus*		-29	-94	6	7.79	<.001	<.001	2604	2.53
L	Middle Occipital Gyrus*	18	-27	-88	14	6.96	<.001	<.001	2604	2.26
R	Middle Occipital Gyrus*	19	29	-90	12	6.44	<.001	<.001	2660	2.09
R	Middle Occipital Gyrus	18	37	-90	2	5.59	<.001	<.001	2660	1.81
R	Inferior Occipital Gyrus*	17	15	-92	-2	7.78	<.001	<.001	2660	2.52
R	Inferior Occipital Gyrus	18	35	-92	-2	5.67	<.001	<.001	2660	1.84
L	Fusiform Gyrus*	37	-49	-60	-12	7.18	<.001	<.001	2604	2.33
R	Fusiform Gyrus	19	39	-82	-8	5.20	<.001	<.001	2660	1.69
R	Fusiform Gyrus	37	43	-62	-14	5.07	<.001	<.001	2660	1.64
R	Fusiform Gyrus	37	55	-48	-14	3.91	<.001	<.001	2660	1.27
R	Superior Parietal Lobule	7	27	-60	50	5.35	<.001	<.001	2660	1.74
R	Precuneus	7	29	-64	44	4.93	<.001	<.001	2660	1.60
R	Precuneus	31	29	-72	22	4.27	<.001	<.001	2660	1.39
R	Precuneus	31	29	-68	30	4.22	<.001	<.001	2660	1.37
L	Cerebellum (Declive)*		-21	-86	-14	7.15	<.001	<.001	2604	2.32
L	Cerebellum (Declive)		-39	-72	-14	5.36	<.001	<.001	2604	1.74
R	Cerebellum (Declive)		25	-78	-12	5.83	<.001	<.001	2660	1.89
R	Cerebellum (Declive)		19	-80	-14	5.76	<.001	<.001	2660	1.87
RPE (Emotional > Neutral faces)										
no significant voxels										

Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
RPE (Emotional < Neutral faces)										
no significant voxels										

Corresponding coordinates for each brain region listed represent the peak voxels for each corresponding region within each significant cluster. All areas reported were found to be significant at a family wise error cluster level corrected threshold of <.05 after running a whole brain analysis at an uncorrected threshold of *p*<.001; k = cluster size; BA = Brodmann's Area
Effect sizes were calculated using Cohen's d

3.3.2.2.3 RPE FOR ROPINIROLE VERSUS PLACEBO

3.3.2.2.3.1 RPE FOR EMOTIONALLY VALENCED AND NEUTRAL FACES (ROPINIROLE VERSUS PLACEBO)

When looking at differences in neural activity correlating with RPE after placebo versus ropinirole administration across both blocks including both emotionally valenced faces and neutral faces, no differences in neural activity were observed even after using SVC within the striatum and ventral striatum.

3.3.2.2.3.2 RPE FOR EMOTIONALLY VALENCED FACES (ROPINIROLE VERSUS PLACEBO)

When looking at differences in neural activity correlating with RPE after placebo versus ropinirole administration across blocks including emotionally valenced faces, no differences in neural activity were observed even after using SVC within the striatum and ventral striatum.

3.3.2.2.3.3 RPE FOR NEUTRAL FACES (ROPINIROLE VERSUS PLACEBO)

When looking at differences in neural activity correlating with RPE after placebo versus ropinirole administration across blocks including neutral faces, no differences in neural activity were observed even after using SVC within the striatum and ventral striatum.

3.3.2.2.3.4 RPE FOR INTERACTION BETWEEN EMOTIONALLY VALENCED AND NEUTRAL FACES AND DRUG (ROPINIROLE VERSUS PLACEBO)

When looking at interaction effects for neural activity correlating with RPE between blocks including emotionally valenced faces and neutral faces after placebo administration and ropinirole administration, no differences in neural activity were observed even after using SVC within the striatum and ventral striatum.

3.3.2.2.4 RPE FOR AMISULPRIDE VERSUS PLACEBO

3.3.2.2.4.1 RPE FOR EMOTIONALLY VALENCED AND NEUTRAL FACES (AMISULPRIDE VERSUS PLACEBO)

When looking at differences in neural activity correlating with RPE after placebo versus amisulpride administration across both blocks including both emotionally valenced

faces and neutral faces, no differences in neural activity were observed even after using SVC within the striatum and ventral striatum.

3.3.2.2.4.2 RPE FOR EMOTIONALLY VALENCED FACES (AMISULPRIDE VERSUS PLACEBO)

When looking at differences in neural activity correlating with RPE across blocks including emotionally valenced faces after placebo and amisulpride administration, no differences in neural activity were observed even after using SVC within the striatum and ventral striatum.

3.3.2.2.4.3 RPE FOR NEUTRAL FACES (AMISULPRIDE VERSUS PLACEBO)

When looking at differences in neural activity correlating with RPE across blocks including neutral faces after placebo administration versus amisulpride administration, an increase in neural activity after amisulpride administration relative to placebo administration is observed in the bilateral vmPFC extending to dmPFC (Figure 3.14 and TABLE 3.8). An ROI analysis using SVC was also carried out in the striatum and ventral striatum however, however, no significant neural activity was found.

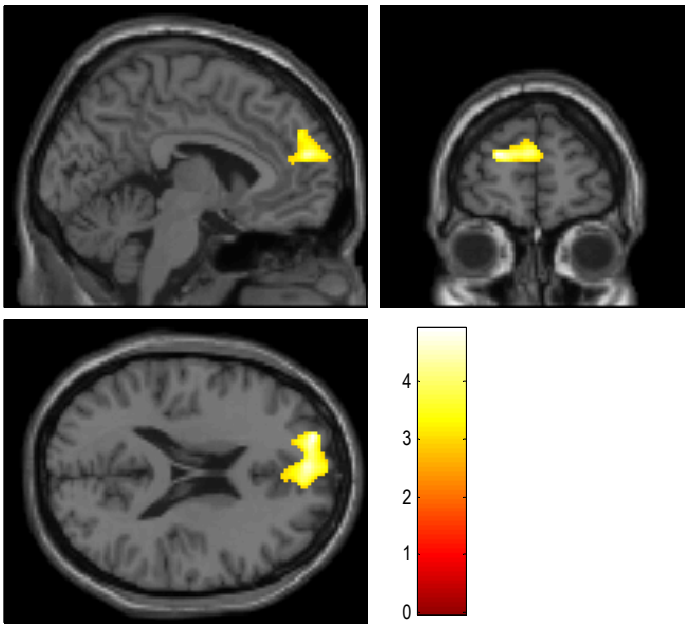

FIGURE 3.14 - Neural activity correlating with RPE when looking at amisulpride versus placebo administration when deciding between two neutral faces This image is shown at an uncorrected height threshold of $p < 0.001$ with an extent threshold of 100 and only clusters surviving FWE cluster-level correction of $p < 0.05$

3.3.2.2.4.4 RPE FOR INTERACTION BETWEEN EMOTIONALLY VALENCED AND NEUTRAL FACES AND DRUG (AMISULPRIDE VERSUS PLACEBO)

When looking at differences in neural activity correlating with RPE between blocks including emotionally valenced faces and neutral faces after placebo administration and amisulpride administration, no differences in neural activity were observed even after using SVC within the striatum and ventral striatum.

TABLE 3.8 - Neural activity correlating with RPE for amisulpride versus placebo

Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
RPE (Neutral faces)										
Placebo < Amisulpride										
L	SFG (vmPFC)	10	-21	58	20	4.91	<.001	0.041	909	1.59
L	SFG (vmPFC)	10	-13	66	14	3.33	0.002	0.041	909	1.08
R	SFG	6	13	42	50	3.77	0.001	0.041	909	1.22
R	SFG (dmPFC)	8	11	48	46	3.18	0.002	0.041	909	1.03
L	MFG (dmPFC)	9	-3	56	20	4.53	<.001	0.041	909	1.47
L	MFG (dmPFC)	9	1	52	24	4.40	<.001	0.041	909	1.43
R	MFG (dmPFC)	8	11	48	36	4.50	<.001	0.041	909	1.46

Corresponding coordinates for each brain region listed represent the peak voxels for each corresponding region within each significant cluster. All areas reported were found to be significant at a family wise error cluster level corrected threshold of <.05 after running a whole brain analysis at an uncorrected threshold of *p*<.005. SFG = Superior Frontal Gyrus; MFG = Medial Frontal Gyrus; vmPFC = ventral medial prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; BA = Brodmann's Area; k = cluster size
Effect size is calculated using Cohen's d

3.4 DISCUSSION

This chapter explores the effect of dopaminergic manipulation on decision-making in an associative learning task in healthy individuals using emotionally valenced and neutral faces as social variables. Our findings demonstrate that the bias toward selecting the positively valenced emotional faces (i.e. happy faces) can be attenuated using dopamine perturbation by both ropinirole and amisulpride and that, after receiving ropinirole, this attenuation is accompanied by increased neural activity

within the dmPFC and dACC, areas suggested to be involved in appraisal (Maier et al., 2012) and emotional processing (Phan et al., 2002a) as well as being a target of D_2 binding during executive decision-making (Ko et al., 2009; Lumme et al., 2006). There is also an attenuation of neural activity within the amygdala, a region associated with emotional processing (Costafreda et al., 2008; Pessoa and Adolphs, 2010; Sergerie et al., 2008) and part of the mesolimbic dopamine pathway (Koob and Swerdlow, 1988). This suggests that dopamine may act to attenuate bias by increasing conflict monitoring while attenuating the biological significance of emotional stimuli.

As predicted, healthy individuals were able to perform this task significantly above chance across all drug conditions and, after being administered a placebo, subjects demonstrated the same bias as previously shown toward picking the happy face even when evidence supported the angry face as the more optimal choice (Averbeck and Duchaine, 2009; Evans et al., 2011a; Furl et al., 2012). As expected, dopamine perturbation had a mitigating effect on the degree of bias exhibited toward the happy face such that, after being administered amisulpride, this bias was attenuated to only trend level significance and, after receiving ropinirole, this bias was completely attenuated so that subjects demonstrated no preference for choosing either the happy or angry face. Although performance was not significantly enhanced by either drug relative to a placebo, the attenuation of a significant bias toward either face demonstrates that both drugs were able to aid subjects to perform more in line with an ideal observer without being biased by emotionally valence suggesting that dopaminergic perturbation may affect behaviour by potentially reducing the social salience of emotionally valenced faces.

This is further supported by the finding that, while deciding between emotional faces, ropinirole attenuated neural activity in the amygdala, an area shown to be involved in emotional processing, especially in regard to facial expression (Costafreda et al., 2008; Pessoa and Adolphs, 2010; Sergerie et al., 2008) and is also considered a major target of midbrain dopaminergic neurons (Fried et al., 2001). One suggestion for the amygdala's involvement in emotional processing is that it is involved in determining the biological significance of emotional stimuli such that more behaviourally relevant stimuli increase the neural response of the amygdala (Pessoa and Adolphs, 2010). Attenuation of the amygdala in this task may show that subjects are able to recognise that the stimuli are not behaviourally relevant and are able to dissociate the probabilities of each face being associated with a win during decision-making from the social and emotional valence of each image.

Furthermore, this attenuation of bias after receiving ropinirole was accompanied by an increase in neural activity within the dmPFC and dACC. In addition to being a target of dopamine (Paus, 2001), the ACC has been shown to help track reward and choice outcome (Holroyd and Coles, 2002), is important in conflict monitoring (Botvinick, 2007) and, along with the dmPFC, aids in action and outcome monitoring (Matsumoto et al., 2007; Walton et al., 2004), appraisal (Maier et al., 2012) and emotional processing (Phan et al., 2002a). Additionally, the dACC has been shown to be a target of D_2 binding during executive decision-making (Ko et al., 2009; Lumme et al.) as an area of output from the mesolimbic dopamine pathway (Vogt and Gabriel, 1993). As dopamine, the dACC and the dmPFC are related to reward related learning, dopaminergic manipulation may affect reward related behaviour and reinforcement learning through increasing neural activity in these regions. Increases in D_2 dopamine

should lead to higher performance on reinforcement learning tasks where more action contingencies are recognised and reinforced by dopamine while decreases in dopamine should have a negative effect on learning action contingencies through depleted neural activity. This has been demonstrated in rats where, after being given dopamine antagonists, they have difficulty linking rewards to certain behaviours (Parkinson et al., 2002) while dopamine agonists help in the "stamping in" of reward contingencies (Wise, 2004). In this task, augmented activity in the dACC and dmPFC after ropinirole administration compared to placebo administration when deciding which was the most rewarding face between two emotional faces may be indicative that increases in dopamine also increases sensitivity to reward contingencies without regard to emotional salience and enhances conflict monitoring coupled with these associations.

To test the association between bias and neural activity, mean neural activity within the dACC and dmPFC which showed significantly greater neural activity after ropinirole administration compared to a placebo was extracted and compared to the bias measures. Change in bias was not found to correlate with the change in neural activity within this region, however, baseline bias, measured as bias without dopaminergic perturbation (i.e. after placebo administration), was found to positively correlate with baseline neural activity when deciding between two emotionally valenced faces as well as negatively correlating with the change in neural activity after ropinirole administration. This suggests that those with greater degrees of baseline bias exhibit higher levels of neural activity within the dACC/dmPFC and that they also show less change in neural activity after ropinirole administration. Meaning, those with less baseline bias exhibit higher neural activity after ropinirole administration albeit

without an accompanying change in bias. It is also possible that no change in neural activity was seen in some participants after taking ropinirole as those with already high levels of neural activity in the placebo condition had already reached a peak in their neural activity so that no amount of perturbation could cause an increase in neural activity. Interestingly, bias measures in the ropinirole condition did not correlate with neural activity suggesting that this increase in neural activity happened independent of bias and change in bias and suggests a general increase in conflict monitoring and appraisal after ropinirole administration.

Another interesting finding in this study was that when deciding between two neutral faces amisulpride attenuated activity in the bilateral cerebellum extending through the tentorium into the right fusiform gyrus and right parahippocampal gyrus compared to a placebo when deciding which face is more likely to be rewarded between two neutral faces. The fusiform gyrus has been shown to be an important area in the implicit processing and identification of faces (Fairhall and Ishai, 2007; Grill-Spector et al., 2004; Haxby et al., 2000; McCarthy et al., 1997c), and the cerebellum has also been found to be involved in social processing (Van Overwalle et al., 2014). Greater activation of these regions when deciding between two neutral faces but not when deciding between two emotional faces in the placebo condition may be indicative of participants recruiting areas more selective to the identification of the face rather than its emotion or either a decrease in attention toward emotionally valenced faces. This is further supported by the fact that when just looking within the placebo condition during decision-making between neutral faces, the right fusiform gyrus is also more active than when deciding between emotionally valenced faces and, in our previous study looking at only emotional faces, this area was not significantly activated (Evans

et al., 2011a), thus supporting a role more closely tied to facial identification than emotional processing.

Although our study did not find any correlation between neural activity and RPE within the ventral striatum based on an ideal observer, this may be because our models did not incorporate values that take into account inherent behavioural biases such as the social salience of faces and the natural discounting of trials further in the past. The model used only looked at optimal performance that would only have been feasible with perfect memory retention and no bias toward emotionally valenced faces. Meaning, this model did not take into account behaviourally mitigating factors such as how choosing a happy face may have provided its own implicit reward as suggested by previous studies (Averbeck and Duchaine, 2009; Evans et al., 2011a). The ideal observer implemented in this study assumes that participants will learn from positive feedback and negative feedback equally to adjust their decisions. Although the difference between feedback and expected reward seem to affect areas tied to dopamine (Glimcher, 2011), learning from positive and negative feedback appears to take place in disparate areas of the brain (Zanolie et al., 2008) and subjects are not able to integrate negative feedback as well as positive feedback (Pessiglione et al., 2006). All other studies exploring the neural effects of dopaminergic manipulation so far have made use of more sophisticated models of behaviour using algorithms such as Q-learning. Despite the ability of our participants to correspond with the ideal observer over a substantial number of trials, to confirm if reward had similar effects as other studies in our experiment, it may be helpful to explore different ways to model how subjects made their decisions. However, the goal of this work was to show how general reward associations may affect neural activity so the RPE calculations were

designed to be simple reward associations. Additionally, as a fairly strict preprocessing routine was implemented, small dropout within regions of the ventral striatum were observed outside of the final mask thus we cannot rule out that perhaps the signal of those regions most affected by our RPE were not picked up by the imaging paradigm implemented.

Although it was hypothesised that ropinirole and amisulpride would act on neural activity in opposing directions especially within the ACC during decision-making and the striatum when processing reward, only ropinirole showed a significant difference to placebo in a region of the ACC when deciding between two emotionally valenced faces. Unexpectedly, neither drug appeared to have an effect on RPE compared to a placebo. In previous studies, dopamine has also been shown to have differential effects on a variety of subjects based on their baseline levels of performance where dopamine has an inverted U effect on cognition (Cools and D'Esposito, 2011; Gjedde et al., 2010; Monte-Silva et al., 2009). Participants who perform well at baseline will perform worse if dopamine is altered too much in either direction while participants who perform poorly at baseline will improve with dopamine agonists. However, if dopamine is increased too much, this performance will degrade once again. It is possible that manipulating dopamine in our subjects had differential effects on their location in this inverted U curve, such that, for some participants, dopamine antagonists had beneficial effects over performance while, for others, dopamine agonists enhanced performance. Thus the lack of significant findings may be explained by a potentially large heterogeneity within our sample relating to baseline dopaminergic levels.

This study was limited by the fact that the concentration of dopamine was not standardised to each person. Dopamine agonists and antagonists were given as fixed doses at fixed intervals to all individuals in the study but, due to individual variances in size age and metabolism, each drug may have affected some more than others. Furthermore levels within the bloodstream have also been shown to be affected by fat content consumed throughout the day. Although care was taken to provide our subjects with qualitatively similar low-fat meals while they were at the institute and instructions were given for appropriate meals on the testing day, it was not possible to control what they had eaten before they attended the testing session. Therefore some of the peak concentrations of some individuals may have been different than for others. Additionally, plasma levels were not recorded so it is impossible to tell how affected each individual was by the dopamine perturbation. Future work could benefit from recording individual plasma concentrations throughout the day and dosing each participant accordingly to ensure that each participant received a standardised dose of medication dependent on their weight.

In theory, administering dopamine agonists should increase the amount of dopamine available in the synapses and thus increase sensitivity to reward, however this is not what all studies have shown. An increasing number of studies report conflicting findings for the mediating effects of dopaminergic manipulation on neural activity. Where some studies report increases in RPE responses in the striatum after administering dopamine agonists and a decrease from dopamine antagonists (Pessiglione et al., 2006), others report increases in the striatum correlating with RPE after giving a dopamine antagonist (Jocham et al., 2011). Furthermore, in one study, treatment with an antagonist in addition to an agonist, did not change the effect of the

dopamine agonist on RPE (Bernacer et al., 2013). These studies show that the effects of dopaminergic manipulation on neural activity is still not well understood and can have a range of effects. Two lines of reasoning prevail when looking at why differential effects may be observed when administering dopamine agonists and antagonists in different studies. The first complication arises from the presence of autoreceptors or receptors which are capable of providing their own negative feedback without further neurochemical perturbation along the neuron and act to control the synthesis and release of neurotransmitters, such as dopamine, mainly in the nigrostriatal and mesolimbic systems (Meltzer, 1980). Autoreceptors are capable of reducing phasic dopamine release through inhibitory feedback (Fasano et al., 2010; Grace, 1991) and are aided by dopamine's increased affinity for presynaptic receptors over postsynaptic receptors (Nemeroff, 2004). In line with this, previous studies have demonstrated how low doses of dopamine agonists can inhibit reinforcement learning (Pizzagalli et al., 2008; Santesso et al., 2009) and reduce phasic dopamine release (Schmitz et al., 2003; Tissari et al., 1983). Although autoreceptors are mainly reported to be affected by dopamine agonists, studies using dopamine antagonists have also reported that they had an effect on neural activity. This was demonstrated by one study using low doses of amisulpride also purported that the presence of autoreceptors acted to augment neural activity in the striatum in response to reward prediction error (Jocham et al., 2011). The second line of reasoning is that dopamine has differential effects on individuals based on their baseline levels of dopamine availability such that the administration of dopamine agonists and antagonists creates an inverted U effect on cognition (Cools and D'Esposito, 2011; Monte-Silva et al., 2009) where alterations in dopamine that oversaturate the system lead to similar deficits observed when dopamine is under-saturated in the synapses. Therefore, administration of dopamine

agonists may increase the presence of autoreceptors which act to attenuate the dopaminergic response or dopamine agonists could be oversaturating dopamine release in the synapses leading to similar performance and neural activation as seen with dopamine antagonists and the inverse could be true for dopamine antagonists.

Overall, this study showed that healthy participants who have been administered both ropinirole and amisulpride show changes in both behaviour and neural activity reflected by an attenuation of bias toward choosing a happy face. This was accompanied by an increase in neural activity within the dACC/dmPFC after ropinirole administration indicative of an increase in conflict monitoring and a decrease in neural activity in the amygdala indicative of a decrease in the attribution of biological significance toward the emotional faces. After amisulpride administration, healthy participants demonstrate an attenuation of neural activity in the cerebellum extending through the tentorium into the right fusiform gyrus but only when deciding between two neutral faces which may demonstrate attenuation in the way participants process facial identification.

CHAPTER 4 - THE NEURAL CORRELATES OF DECISION-MAKING DURING AN ASSOCIATIVE LEARNING TASK WITH A SOCIAL COMPONENT – IN PATIENTS WITH SCHIZOPHRENIA

4.1 BACKGROUND

Patients with schizophrenia show aberrant patterns of neural activation across a range of cognitive tasks from executive functioning (Minzenberg et al., 2009), decision-making (Paulus et al., 2002; Rausch et al., 2014), processing of emotional faces (Gur et al., 2002; Takahashi et al., 2004) to viewing and encoding reward (Gradin et al., 2011; Murray et al., 2008; Nielsen et al., 2012), compared to healthy controls. These differences are apparent even when controlling for medication effects (Sugranyes et al., 2011). Although most of these tasks show diminished neural activity, a number of studies in patients with schizophrenia also show increased neural activity in neural areas relating to decision-making, emotional and reward processing (Dyck et al., 2014; Thormodsen et al., 2011). Furthermore, aberrant neural activity in patients with schizophrenia, both as increases and decreases, has been found despite similar behavioural task performance as controls, particularly in tasks looking at associative learning (Murray et al., 2010) suggesting that patients with schizophrenia may recruit compensatory networks to make up for aberrant processing in other neural areas.

Together, both decreased and increased neural activity in patients with schizophrenia demonstrate wide-spread differences (Ernst and Paulus, 2005a), which may be mediated through aberrant dopaminergic processing in schizophrenia (Howes and Kapur, 2009; Rolls et al., 2008). Various lines of research, which are outlined in more detail in Chapter 1 (page 16), have shown that that higher presynaptic dopamine levels in the mesolimbic dopaminergic system - involving more striatal and limbic areas - may

lead to psychotic symptoms and decreased levels of dopamine in the mesocortical system - involving more prefrontal areas - are believed to lead to negative and affective symptoms (Howes and Kapur, 2009; Kapur, 2003). As dopamine plays a significant role in decision-making, by aiding in both value formation, or the conceptualisation of value in terms of the costs and benefits of a given option or set of options, and updating of predictions about rewards to inform decisions (Schultz, 2006), disruption to this system in schizophrenia may also lead to aberrant decision-making by altering the salience of informational stimuli (Berridge, 2012; Kapur, 2003). This means that, in schizophrenia, abnormal dopamine responses to stimuli, which would otherwise be innocuous, may lead to the incorrect assertion that these stimuli are more important than they actually are. This, in turn, may lead to the aberrant encoding, or classification, of stimuli and consequently to the formation of false beliefs. For example, a patient with schizophrenia might falsely perceive that what a character is saying in a television series is a personal message to them due to them attributing aberrant salience to the stimuli. In this case, the increased salience given to otherwise innocuous speech is interpreted with higher personal meaning as it is perceived as holding greater importance. This affects how patients with schizophrenia interact with the environment by impacting on how they weigh information in order to make decisions. As described in chapter 3 (page 56), the salience of stimuli can help guide decisions by coding their importance (Berridge, 2012) thus, aberrant attribution of salience to certain stimuli can lead to aberrant decision-making.

In schizophrenia, the altered attribution of salience to stimuli means that the affective appraisal of social stimuli is often different to that of healthy controls and thus may lead to altered decision-making. This is particularly important when faced with social,

or interpersonal, stimuli, such as discerning the emotion of another person or interpreting the meaning of what another person is saying; decision-making requires the affective, or emotional, appraisal of options to evaluate the respective value of different stimuli which is governed by both automatic and conscious processes (Ernst and Paulus, 2005a). Currently, most paradigms addressing salience during decision-making tasks incorporate non-social elements to determine general decision-making biases.

One such method of assessing the salience of stimuli is by determining the expected value of a reward for a given specific stimuli. The higher the magnitude of the expected value, the more salient the stimuli should become. Using the magnitude of the expected value and the resulting reward gained from picking a certain stimulus, it is possible to calculate the difference between the expected value of a stimulus and the actual value after picking it. This difference between actual reward and expected reward is known as the reward prediction error and has been used with increasing frequency in studies looking at how dopamine affects decision making. As dopaminergic activity is dependent on both reward and reward expectancy, the reward prediction signal has been shown to correlate with neural activity in dopamine rich areas, such as the striatum (Glimcher, 2011; Schultz, 1998). In schizophrenia, neural prediction error responses have been generally found to be reduced compared to healthy controls, in areas such as the striatum, suggesting that, in schizophrenia, abnormal dopaminergic processing disturbs the encoding and reward processing stages of decision-making (Gradin et al., 2011; Morris et al., 2012; Murray et al., 2008). However, patients with schizophrenia also show exaggerated neural activity within the ventral striatum in response to expected rewards but diminished responses in the

ventral striatum associated with unexpected rewards (Morris et al., 2012). This suggests that patients may disproportionately weight positive reward which may affect how they make decisions.

As social information plays an important role in making decisions when interacting with others, this current study aims to expand on previous work which explored how facial valence affected decision-making in the same associative learning task described in chapter 3 (page 64) where subjects were presented with two faces, either a happy face and an angry face of the same identity or two neutral faces of different identities. They were then asked to determine through trial and error which of the two faces was being financially rewarded the most often.

Using this task previously showed that, when deciding which face was most likely to be rewarded between a happy and angry face, both healthy controls and patients with schizophrenia were biased toward picking a happy face even when evidence supported the angry face as the better option (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2011b; Furl et al., 2012). Furthermore, when evidence strongly favoured the angry face, patients with schizophrenia showed greater aversion toward picking the angry face than healthy controls (Evans et al., 2011b). This implies that positive social cues are valued to a greater extent in patients with schizophrenia and that both groups are more averse toward picking the angry face.

This current study aims to expand on this previous work using fMRI by examining the differences in neural activity in patients with schizophrenia versus healthy controls in this same task (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2011b) as well as incorporating in a condition looking at decision-making between two neutral faces in order to explore the effects of decision-making on social stimuli without

varying social salience. The main analyses will investigate the differences in neural activity during decision-making and the processing of RPE between patients with schizophrenia and healthy controls who have taken a placebo. Furthermore, as dopamine is considered an important aetiological factor in the manifestation and treatment of schizophrenia, this study will also explore how changes in neural activity due to dopaminergic perturbation in healthy controls using a dopamine agonist, ropinirole, antagonist, amisulpride, evaluated against a placebo compares to changes in neural activity in patients with schizophrenia.

In light of previous research, I hypothesise that:

1. In line with Evans et al. (2011b), patients with schizophrenia will demonstrate the same bias as previously shown toward picking the more positively valenced happy face even when evidence supports the more negatively valenced angry face as the most likely to be rewarded. Patients with schizophrenia will not be biased toward either of the neutral identities. Furthermore, any decision-making bias will not be due to poor task performance as patients will perform this task significantly above chance and will not significantly differ in performance to healthy controls, as previously shown (Evans et al., 2011b).

2. When compared to healthy controls who have taken a placebo, patients with schizophrenia will show decreased neural activity during decision-making, which will be apparent within various regions associated with decision-making and emotional processing such as the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), thalamus, posterior cingulate cortex (PCC), and amygdala as well as reward related decision-making regions such as the caudate and putamen.

3. When processing RPE related to their decisions (i.e. the difference between expected reward and actual reward), patients with schizophrenia will also show some activation of the ventral striatum, a region high number in dopamine receptors, in response to RPE albeit to a significantly lesser extent than healthy controls as demonstrated in other decision-making studies (Gradin et al., 2011; Morris et al., 2012; Murray et al., 2008).

4. Within the regions shown to be perturbed by dopaminergic manipulation in Chapter 3, in comparison to healthy controls who have received a placebo, patients with schizophrenia will show similar patterns of neural activity as healthy controls who had received amisulpride as both groups will have been under the influence of dopamine antagonists. Following this, patients with schizophrenia will show the opposite pattern of neural activity as healthy controls who had been administered ropinirole such that where ropinirole increased neural activity in healthy controls, patients will show decreased neural activity.

5. Further to the previous hypothesis, looking within regions which show altered neural activity between patients with schizophrenia and healthy controls who have taken a placebo, when looking in healthy participants only, these same regions will show increases in neural activity after ropinirole administration and decreases in neural activity after amisulpride administration.

4.2 METHODS

4.2.1 PARTICIPANTS

In addition to the 20 right-handed healthy controls (17 males) which were described in chapter 3 (page 63), 48 right-handed patients with schizophrenia and schizoaffective

disorder (39 males), diagnosed according to ICD-10 (Organization, 1992), comprised the current sample. Seven of the patients with schizophrenia dropped out of the study before completing scanning, leaving a final sample of 42 patients with schizophrenia (33 males). Intelligence quotient (IQ) was estimated in all participants using the two-item Wechsler Abbreviated Scale of Intelligence (WASI) consisting of the vocabulary and matrix reasoning subtests (Wechsler, 1999). Demographic information can be found below in Table 4.1. All participants signed informed consent and were compensated for their participation in the study on completion of the testing. Ethical approval was obtained from the Central London Research and Ethics Committee 3. Further details of recruitment and inclusion and exclusion criteria can be found in Chapter 2 (page 35).

TABLE 4.1 - Demographic and clinical sample characteristics

	Patients with schizophrenia (N=42) (mean (SD))	**Healthy Controls** (N=20) (mean (SD))	**Statistics**
Age (years)	37.36 (8.82)	36.25 (9.41)	$t(60) = 0.45$, $p > 0.1$
WASI IQ	97.10 (14.89)	107.30 (14.42)	$t(60) = 2.55$, $p = 0.013$
NS-SeC	2.79 (1.63)	2.35 (1.60)	$\chi^2(4) = 5.79$, $p > 0.1$
Gender	33M, 9F	18M, 2F	$\chi^2(1) = 0.36$, $p > 0.1$
Age at onset (years)	23.76 (5.80)	-	
Duration of illness (years)	13.54 (8.76)	-	
CPZ equivalents	473.93 (393.15)	-	
PANSS		-	
Positive Symptoms	16.18 (4.37)	-	
Negative Symptoms	18.28 (5.48)	-	
General Symptoms	31.13 (6.95)	-	
Total	65.58 (13.89)	-	

IQ = Intelligence quotient; M = Male; F = Female.

WASI = Wechsler Abbreviated Scale of Intelligence

ns-sec = National Statistics Socio-economic Classification

CPZ = Chlorpromazine equivalent (Woods, 2003; Bazire, 2005).

PANSS = Positive and Negative Symptom Scale

4.2.2 TASK

The task used was a forced-choice, stochastically rewarded decision-making task incorporating faces of varying social valence. In each trial two faces were presented to the left and the right of the screen. Pairs consisted of either: a happy face and an angry face of the same identity, or of two neutral faces of differing identities. Each visit consisted of two scanning sessions comprised of four counterbalanced blocks of 30 trials each (Figure 2.5, page 47). Pairs of emotionally valenced stimuli (i.e. happy and angry faces) were alternated with pairs of neutrally valenced stimuli (i.e. neutral faces). Within each emotionally valenced block, the identities of each face were kept consistent but the order of presentation of each identity was counterbalanced across sessions. Each block consisted of 30 trials with the presentation of each face counterbalanced across the left and right sides. Probability estimates were assigned to the faces at the beginning of each trial such that on 60% of the trials one face would win and 40% of trials the other face would win. The probability distribution of each face winning was counterbalanced across blocks such that the angry face won more in half of the blocks and the happy face won more in the other half, and that identity one won more over identity two for half of the blocks and vice versa for both the emotionally valenced and neutral faces. The order of these wins was counterbalanced across the participants and visits. In each trial, participants were instructed to pick the face which, at that time, they believed was the most likely to win. They were told that after making this decision they would be told whether or not they had won where a win would show that they had won 10 pence along with their current winnings total and a loss was associated with no change in winnings and only the message “You lose.” The presentation of stimuli is shown below in Figure 4.1. Further details, including the task instructions, can be found in Chapter 2 (page 44).

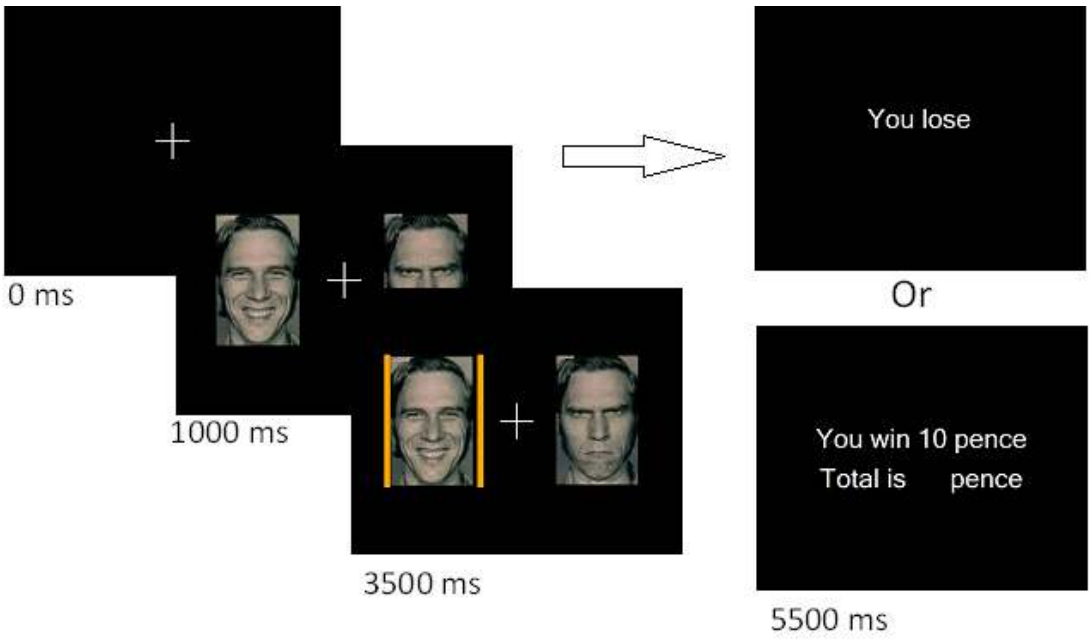

FIGURE 4.1 - Presentation of stimuli in the scanner for each trial

4.2.3 FMRI DATA ACQUISITION

Functional magnetic resonance imaging (fMRI) data were acquired on a Discovery MR750 3T scanner at the Centre for Neuroimaging Sciences, London (T2* weighted gradient-echo echo-planar images (EPIs), repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, flip angle = 75°, 64 x 64 matrix, 24cm field of view). A 12-phase head coil array was used over the whole head for RF transmission and reception. Each whole-brain image contained 38 3-mm axial slices separated by a distance of 0.3 mm with in-plane isotropic voxel resolution of 3.75 x 3.75 mm. For each block, 430 scans were acquired and two sessions were recorded for each participant.

Before the experimental portion of the experiment, a T1-weighted structural scan using a fast-spoiled gradient-echo pulse sequence (TR = 9.356 ms, TE = 3.828 ms, flip angle = 12°, time to inversion = 450 ms) was acquired for reference purposes. The first four volumes were discarded to allow for transient effects.

Participants made their responses using a two buttons on a three button-box with their index and middle fingers of their right hand. Head movement was minimised using headphones and additional padding around the head and ears as well as around the arms and legs.

4.2.4 ANALYSIS

All data were preprocessed and analysed using Statistical Parametric Mapping 12 (SPM12) (Wellcome Department of Imaging Neuroscience, London, UK. www.fil.ion.ucl.ac.uk/spm) and MATLAB R2014a (MathWorks Inc. Sherbon, MA, USA). Further details of these steps can be found in Chapter 2 (page 53).

A general linear model (GLM) was constructed in SPM12 to analyse the images with each event modelled as a delta (stick) function. Each block, consisting of 30 trials, was modelled independently and was defined as being either a block using emotionally valenced faces (e.g. happy and angry faces) or neutral faces (e.g. two faces of different identities). Events of interest within each block included the presentation of the faces, a decision-making regressor indicating when the decision was made for which face the subject believed would be rewarded (determined by a button press), and the feedback presentation within each trial. Also modelled were regressors to represent the motion parameters as well as parametric modulators on the decision-making regressor for the probability of each face chosen being associated with a win and feedback regressors. The probability that the face they picked would win was calculated using an ideal observer. The calculations used to determine this probability are outlined in depth in Chapter 2 (page 47). The feedback regressor, associated with when they were given feedback about whether or not the face they had chosen was associated with a reward, was parametrically modulated by the reward prediction error (RPE)

determined by subtracting the actual reward (i.e. 1 for a win and 0 for a loss) from the predicted probability that the chosen face would win as detailed in Chapter 2 (page 49). Each regressor, except for the motion parameters, was convolved with a canonical hemodynamic response function and its temporal derivative. Missed trials were not modelled as events. Blocks where subjects failed to respond for greater than 50% of the trials were excluded from analysis as they were deemed to be insufficiently attending to the task. Furthermore, without feedback from all trials, it would have been more difficult for subjects to accurately assess which face was winning more often throughout the block. Excluded blocks accounted for 1 block across 1 subject (one block when making decisions between two emotionally valenced faces).

Performance estimates were calculated across all trials by comparing the face the subject picked to the face the ideal observer assigned the highest probability of winning. In the case that both faces had equal probability of winning (i.e. at 50% probability) either face picked was deemed optimal. Overall performance estimates were calculated across all trials as the number of times the participant picked the face deemed optimal over the number of valid trials (i.e. 30 – any misses). These estimates were then averaged across all blocks which were not excluded to get an overall performance estimate for all blocks using emotionally valenced and neutral faces.

To assess how facial expression biased decision-making, all trials were separated into when participants agreed with the ideal observer and when they disagreed with the ideal observer for each facial valence as well as for the two neutral face identities. A 2x2 contingency table was calculated for each block type (i.e. emotionally valenced and neutral) representing choices by the ideal observer and choices by the participant. When the probability for each face winning was ambiguous (i.e. equal probabilities for

both faces), the contingency count for each face was increased by 0.5. Using this table it was possible to calculate the conditional probability of each participant choosing the happy face when they should have chosen the angry face given the current evidence for the angry face *p*(happy|angry) as well as when they chose the angry face when they should have chosen the happy face given the current evidence for the happy face *p*(angry|happy). The difference between these two measures was calculated to represent the degree of bias toward picking the happy face (*p*(happy|angry) – *p*(angry|happy)). This measure indicates how often participants ignore the evidence that has accumulated for the negatively valenced face and chose the positively valenced face compared to how often they ignored evidence that had accrued for the positively valenced face and chose the negatively valenced face. This bias distribution was examined across all participants and entered into a one sample t-test to see if it significantly differed from 0. It is important to note these conditional probabilities were calculated separately to the probability that each face would win. A more comprehensive overview with equations is provided in Chapter 2 (page 49). This process has been replicated in multiple studies to represent the degree of bias (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2010; Evans et al., 2011b; Furl et al., 2012).

The main focus of this study was to look at how decision-making and RPE affected neural activity so contrasts were looked at representing neural activity when a button was pressed to indicate which face the participant had chosen on a given trial, here after referred to as the decision-making condition as well as contrasts representing neural activity correlating with RPE given by the parametric modulator on reward feedback. Second-level contrasts between groups were assessed using two sample t-

tests. Within each group comparison (i.e. patients with schizophrenia versus healthy controls), the main effect of task was analysed looking at by combining the blocks for emotionally valenced and neutral faces. Then contrasts were also created for blocks looking at only decision-making between the emotionally valenced faces to assess differences in decision-making with emotionally salient stimuli as well as within only the blocks looking at decision-making between neutral faces to assess differences in decision-making between general social stimuli with no emotional salience. Interaction effects between the emotion and group were also analysed to see if there was any interaction between the emotionally valenced face condition and the neutral face condition and group.

To look at interaction effects between group and emotion an overall examination of blocks looking at the effects of group (i.e. patients with schizophrenia versus healthy controls) and emotion (i.e. emotionally valenced versus neutral faces) were entered into 2x2 full factorial in SPM12 with group and emotion as conditions.

Contrasts were whole brain cluster-level family wise error (FWE) corrected at $p<.05$ with a height threshold of $p < .005$, uncorrected, and an extent threshold of 100 contiguous voxels. Voxels which survived peak level FWE correction at $p<.05$ are also reported. Reported voxels coordinates were converted from Montreal Neurological Institute (mni) coordinates into Talairach coordinates using the function icbm_spm2tal (Laird et al., 2010; Lancaster et al., 2007a) and were entered into Talairach Daemon to confirm their location in gray matter (Lancaster et al., 1997; Lancaster et al., 2000). Questionable results were further visualised by entering the original mni coordinates into xjview (http://www.alivelearn.net/xjview). Results are reported as their original mni coordinates as output by SPM12. If more than one voxel was found to be

significant within a region without *a priori* interest, only the peak voxel is reported. Additionally, the contrast estimates from each image were analysed at the peak voxels to determine the direction of change between each condition analysed as significant decreases under one condition could still appear as increases in another condition even if no change in neural activity was present.

Region of interest analyses were also carried out within regions with an *a priori* interest to our study using small volume correction (SVC) within SPM12. Volumes of interest were defined using WFU PickAtlas Tool (Maldjian et al., 2003) for the amygdala and striatum and the ventral striatum was taken from Mawlawi et al. (2001). Only voxels which survived FWE correction at a peak level of $p < .05$ are reported.

Additionally, in order to compare neural activity in the patients with schizophrenia to regional changes in neural activity from dopaminergic perturbation in healthy controls, Volumes of interest were also defined by creating masks around the clusters which survived FWE cluster level correction in Chapter 3 (pages 79 and 84) within SPM12. These regions were the bilateral dACC/dmPFC from the contrast between ropinirole and placebo administration when deciding between two emotional faces (page 79), and the right cerebellum/fusiform gyrus in the contrast between amisulpride and placebo administration when deciding between two neutral faces (page 84). These masks were used to see if between group effects between patients with schizophrenia and healthy controls could be observed within the same regions after SVC.

Inversely, for all clusters which showed differences between patients with schizophrenia and healthy controls, masks around these volumes of interest were defined using SPM12. These masks were then used in the same contrasts for healthy participants after dopaminergic perturbation to see if similar effects from between

patients with schizophrenia and healthy controls could be observed after SVC within healthy participants who had received ropinirole or amisulpride versus a placebo.

4.3 RESULTS

4.3.1 BEHAVIOURAL ANALYSIS

4.3.1.1 PERFORMANCE DURING DECISION-MAKING

To assess performance in terms of the percentage accordance to an ideal observer, the face picked by the subject on each trial was compared to an ideal observer calculated based on the number of times a face won or would have won over the number of valid trials. Performance estimates across subjects averaged separately across all trials when deciding between two emotionally valenced faces and two neutral faces as well as across each group are shown in Table 4.2, Figure 4.2 and Figure 4.3. On average, both healthy controls and patients with schizophrenia performed above chance levels (p > 0.1). Furthermore, when individual choices were compared to an ideal observer, patients with schizophrenia did not differ significantly in performance from the placebo condition in healthy controls (p > 0.05), when deciding between both emotionally valenced faces and neutral faces Table 4.2. Albeit they did differ from the healthy controls at a trend level significance (p < 0.1) when deciding between two emotionally valenced faces.

TABLE 4.2 - Performance estimates for each group

	Emotional faces	**Neutral faces**	**Statistics between groups**	
	mean (SD)	*mean (SD)*	*Emotional faces*	*Neutral faces*
Patients with Schizophrenia	64.5% (13.0%)	63.5% (11.3%)	t(60) = 1.69, p=0.096†	t(60) = 1.46, p=0.149
Healthy Controls (Placebo)	70.9% (15.7%)	68.9% (17.5%)		

SD = Standard deviation; * = p < 0.05, † = p < 0.1
Performance is measured in terms of percentage accordance to an ideal observer. This is looked at separately across all blocks using emotionally valenced faces and neutral faces; t-values were calculated to look for any significant differences in performance measures between groups.

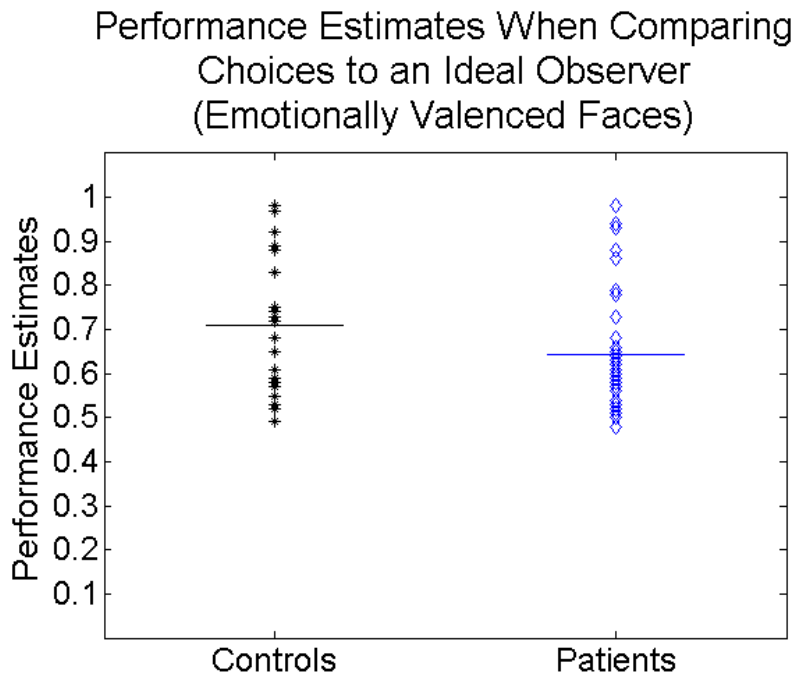

FIGURE 4.2 - Performance estimates across drug conditions when deciding between emotionally valenced faces for healthy controls who have taken a placebo (black) and patients with schizophrenia (blue) where performance is compared to an ideal observer on a trial by trial basis. Each cross represents the performance of a single individual and the line represents the mean across all subjects. Although both groups did not significantly differ in performance, patients performed slightly worse than healthy controls at a trend level.

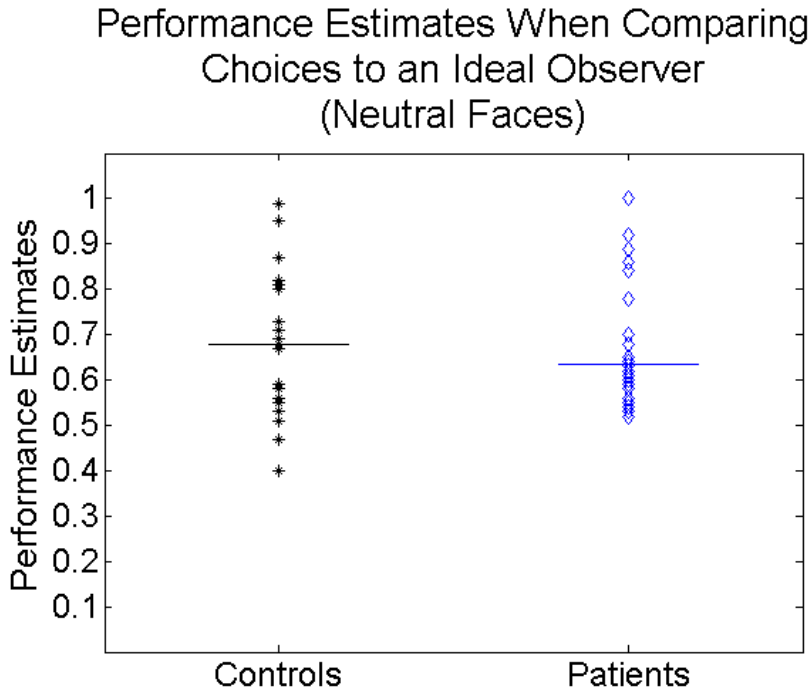

FIGURE 4.3 - Performance estimates across drug conditions when deciding between two neutral faces for healthy controls (black) and patients with schizophrenia (blue) where performance is compared to an ideal observer on a trial by trial basis. Each cross represents the performance of a single individual and the line represents the mean across all subjects. Neither group significantly differed in peformance.

4.3.1.2 BIAS MEASURES

When deciding between two emotionally valenced faces, the distribution of bias toward picking the happy face when evidence supported the angry face as the best choice was found to be significantly different from 0 in the patients with schizophrenia. When deciding between two neutral faces, there was no significant bias toward picking either of the neutral identities in patients with schizophrenia (Table 4.3). No significant differences were found between bias estimates observed in the patients with schizophrenia and the healthy controls who had taken a placebo for either condition ($p > .05$).

TABLE 4.3 - Bias estimates for patients with schizophrenia

	Emotional faces	**Neutral faces**	**Statistics for bias toward**	
	mean (SD)	*mean (SD)*	*Emotional (happy face)*	*Neutral (identity 1)*
Healthy Controls (Placebo)	0.08 (0.11)	-0.07 (0.18)	t(19) = 3.11, p=0.006*	t(19) = 1.82, p=0.085†
Patients with Schizophrenia	0.12 (0.22)	-0.03 (0.18)	t(41) = 3.63, p=0.001*	t(41) = 1.06, p=0.296

* significant at p<0.05, † trend level significance at p<0.1, SD = Standard deviation

Bias estimates are estimated as the degree of bias toward picking one of the faces when the ideal observer supports the other face as the better option using a contingency table described in the methods. Bias significance was calculated as the difference from 0

4.3.2 FMRI ANALYSIS

4.3.2.1 HEALTHY CONTROLS VERSUS PATIENTS WITH SCHIZOPHRENIA DURING DECISION-MAKING

4.3.2.1.1 DECISION-MAKING ACROSS EMOTIONALLY VALENCED FACES AND NEUTRAL FACES

When deciding which face has a higher probability of being rewarded between two emotionally valenced faces and two neutral faces, patients with schizophrenia showed attenuated neural activity compared to healthy controls in the bilateral thalamus extending into the caudate and posterior cingulate (Table 4.4, page 128, Figure 4.4, Figure 4.5) with a peak in the thalamus within the medial dorsal nucleus (MDN) at (x =

5, y = -12, z = 6). Furthermore, even after applying a more stringent height threshold of $p < .05$ FWE corrected, significant peaks remained within the thalamus, posterior cingulate and cerebellum and a cluster of 370 voxels within the thalamus survived cluster level correction at this stringent threshold.

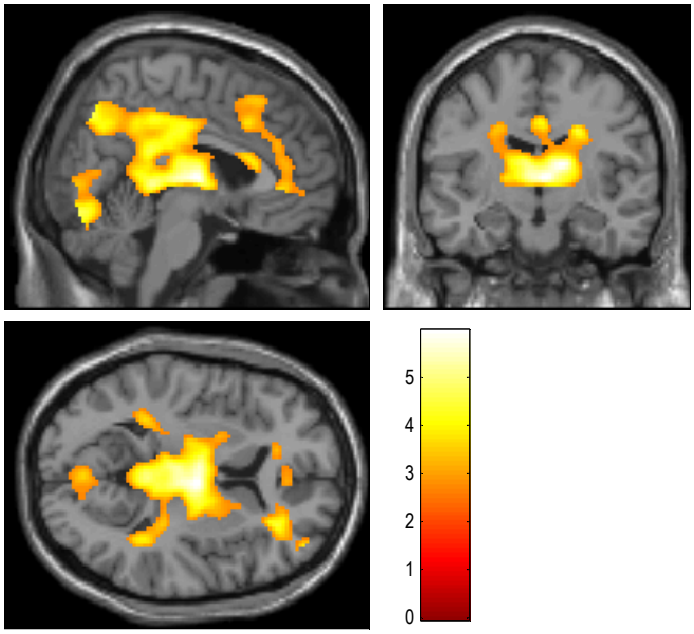

FIGURE 4.4 - Neural activation during decision-making across emotionally valenced and neutral faces for controls (placebo) versus patients with schizophrenia. Peak differences showing greater attenuation of neural activity in patients with schizophrenia than healthy controls were found with a peak in the thalamus (medial dorsal nucleus) at (x = 5, y = -12, z = 6). Results are shown for clusters which survive FWE cluster level correction at $p<.05$ with an uncorrected height threshold of $p<.005$ and an extent threshold of 100.

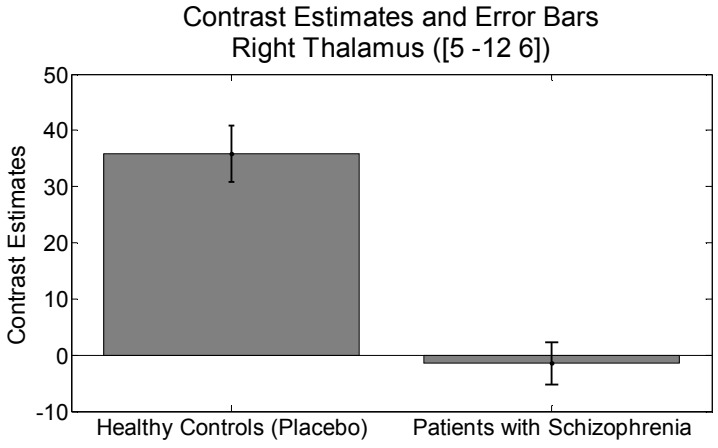

FIGURE 4.5 - Contrast estimates with standard error bars for differences in neural activity in the thalamus for healthy controls and patients with schizophrenia during decision-making across both emotionally valenced and neutral faces. The thalamus is shown here as it represents the peak difference in neural activity between patients with schizophrenia and healthy controls and demonstrates that, neural activity in patients with

schizophrenia did not show any significant changes where healthy controls who had taken a placebo showed robust changes in neural activity while deciding which face was most likely to be rewarded across emotionally valenced faces and neutral faces.

Patients with schizophrenia also showed greater neural activity than healthy controls in the right post- and precentral gyrus (Table 4.4, page 128). However, these effects were not as robust as the findings for attenuated neural activity in patients with schizophrenia compared to healthy controls. Furthermore, this effect was found to be driven by a stronger attenuation of neural activity in the right post- and precentral gyrus in the healthy controls while patients with schizophrenia appeared to show no changes in neural activity within this region.

4.3.2.1.2 DECISION-MAKING BETWEEN EMOTIONALLY VALENCED FACES

When looking at the effect of neural activity when deciding which face has a higher probability of being rewarded between two emotionally valenced faces, patients with schizophrenia showed attenuation of neural activity compared to healthy controls in the bilateral thalamus (Figure 4.6, Figure 4.7, and Table 4.4, page 128). However, the differences between groups were not as significant or as widespread as when comparing decision-making across both emotionally valenced and neutral faces.

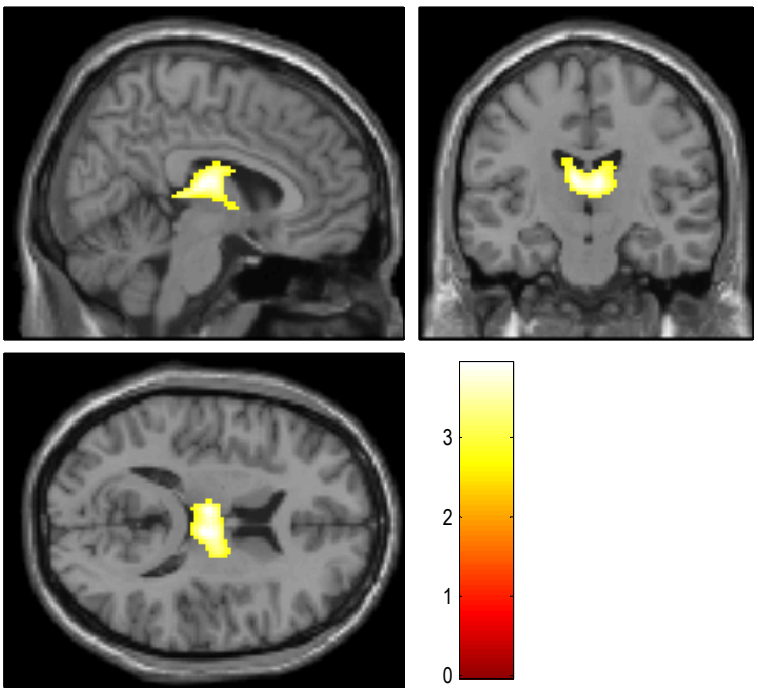

FIGURE 4.6 - Neural activation during decision-making across emotionally valenced faces for controls (placebo) versus patients with schizophrenia. Peak differences were found within the thalamus at (x = 7, y = -16, z = 14) and extended into further regions of the thalamus. Results are shown for clusters which survive FWE cluster level correction at $p<.05$ with an uncorrected height threshold of $p<.005$ and an extent threshold of 100.

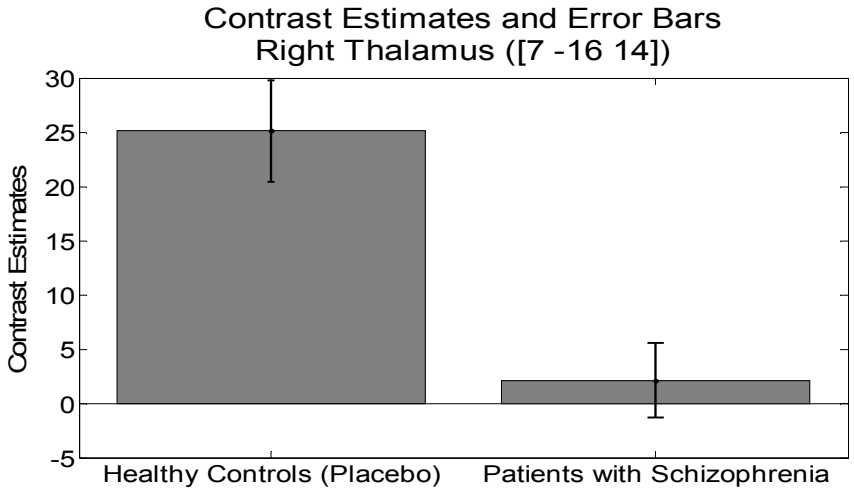

FIGURE 4.7 - Contrast estimates with standard error bars for differences in neural activity in the thalamus for healthy controls and patients with schizophrenia during decision-making across emotionally valenced faces The thalamus is shown here as it represents the peak difference in neural activity between patients with schizophrenia and healthy controls and demonstrates that, neural activity in patients with schizophrenia did not show any significant changes where healthy controls who had taken a placebo showed robust changes in neural activity while deciding which face was most likely to be rewarded between two emotionally valenced faces.

Healthy controls also showed significantly decreased neural activation compared to the patients with schizophrenia in the right pre- and postcentral gyrus, consistent with

the areas seen in the combined contrast comparing neural activation during decision making between groups across emotionally valenced and neutral stimuli (Table 4.4, page 128). This difference was also driven by a stronger decrease in healthy controls with no significant changes in neural activity in patients with schizophrenia.

An ROI analysis using SVC was also performed within the left and right amygdala to see if patients with schizophrenia showed altered neural activity to healthy controls in this region involved in emotional processing when deciding which face was most likely to be rewarded between two emotionally valenced faces. However, no differences were observed.

4.3.2.1.3 DECISION-MAKING BETWEEN NEUTRAL FACES

When looking at the effect of deciding which face has a higher probability of being rewarded between two neutral faces between patients with schizophrenia and healthy controls who have taken a placebo, patients with schizophrenia showed greater attenuation of neural activity than healthy controls in the bilateral thalamus, posterior cingulate cortex (PCC), cuneus, caudate, lingual gyrus and extending through the tentorium into the cerebellum with a peak in the left PCC at (x = -1, y = -36, z = 22) and the right thalamus at (x = 5, y = -12, z = 6). These areas are consistent with the areas showing greater activation in the combined contrast looking at the effect of emotionally valenced and neutral faces only with the addition of the lingual gyrus and extending through the tentorium to show more extensive activation differences in the cerebellum (Table 4.4, page 128 and Figure 4.8). Further analysis revealed that these effects were due to increases in neural activity within the healthy controls with no significant change in neural activity in patients with schizophrenia (Figure 4.8).

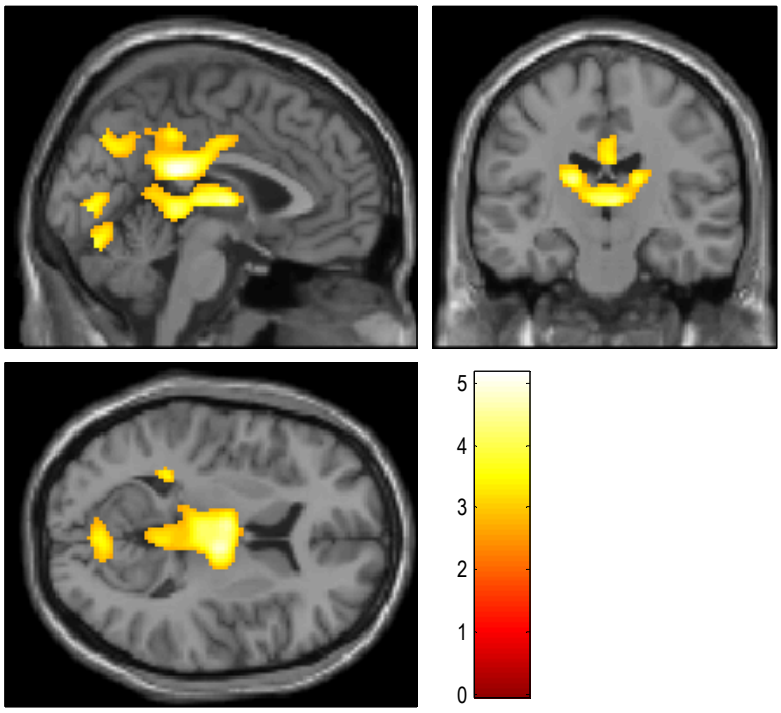

FIGURE 4.8 - Neural activity when deciding between two neutral faces in patients with schizophrenia versus healthy controls on placebo in the thalamus extending into the PCC and through the tentorium into the cerebellum where neural activity is greater in the healthy controls than the patients with schizophrenia. This image is shown at an uncorrected height threshold of $p < 0.005$ with an extent threshold of 100 and only clusters surviving FWE cluster-level correction of $p < 0.05$

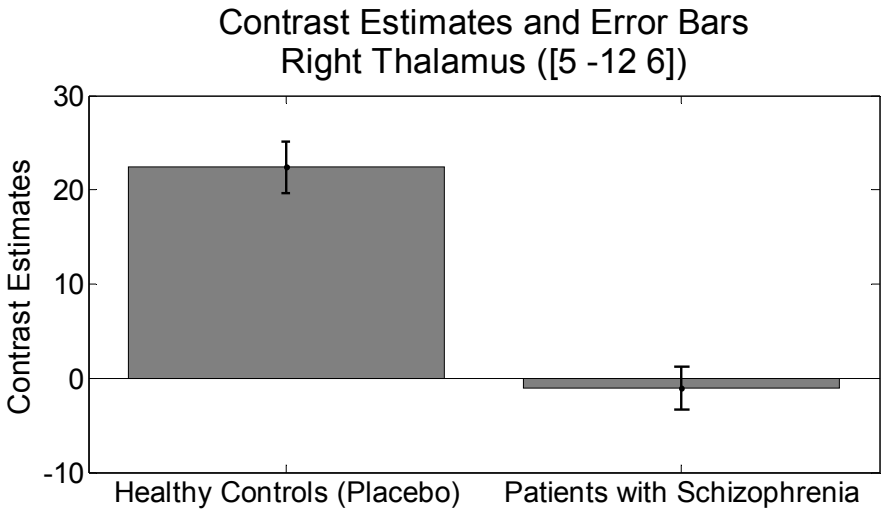

FIGURE 4.9 - Contrast estimates with standard error bars for differences in neural activity in the thalamus for healthy controls and patients with schizophrenia during decision-making across neutral faces The thalamus is shown here as it represents the peak difference in neural activity between patients with schizophrenia and healthy controls and demonstrates that, neural activity in patients with schizophrenia did not show any significant changes where healthy controls who had taken a placebo showed robust changes in neural activity while deciding which face was most likely to be rewarded between two neutral faces.

4.3.2.1.4 INTERACTION BETWEEN THE EMOTIONALLY VALENCED AND NEUTRAL FACES DURING DECISION-MAKING

When looking at the interaction effects between decision-making in using emotion (emotionally valenced versus neutral faces) and group (healthy controls who have taken a placebo versus patients with schizophrenia) there was an interaction effect in the right cuneus and left middle occipital gyrus and lingual gyrus (Table 4.4 and Figure 4.10). Further examination of the changes in neural activity revealed that this effect was driven by an increase in neural activity in the healthy controls between emotionally valenced and neutral faces and an attenuation of neural activity in patients with schizophrenia between emotionally valenced and neutral faces (Figure 4.11).

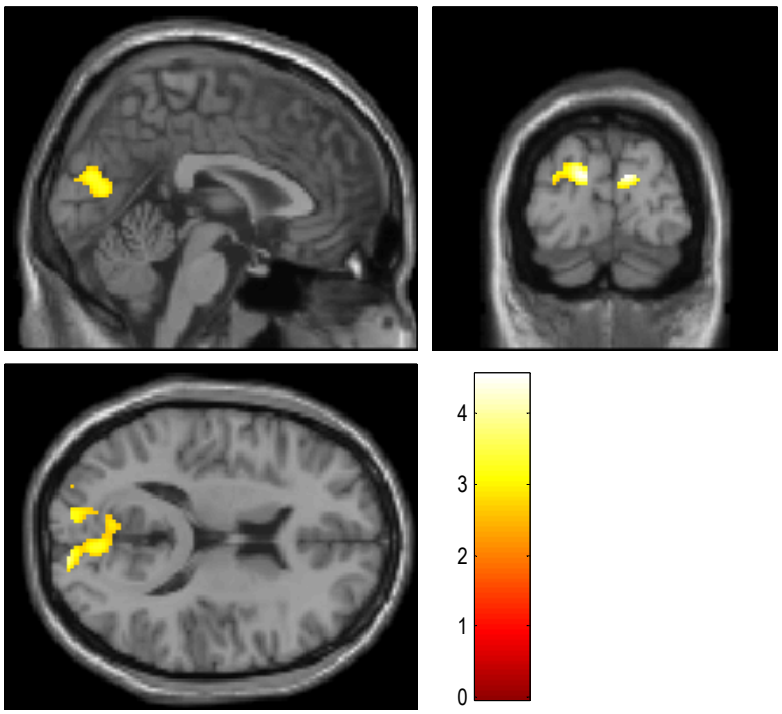

FIGURE 4.10- Neural activity for interaction effects between group (patients with schizophrenia versus healthy controls on placebo) and emotion (emotionally valenced faces versus neutral faces) where neural activity is greater in the healthy controls than the patients with schizophrenia in the right cuneus, left middle occipital gyrus and lingual gyrus. This image is shown at an uncorrected height threshold of $p < 0.005$ with an extent threshold of 100 and only clusters surviving FWE cluster-level correction of $p < 0.05$

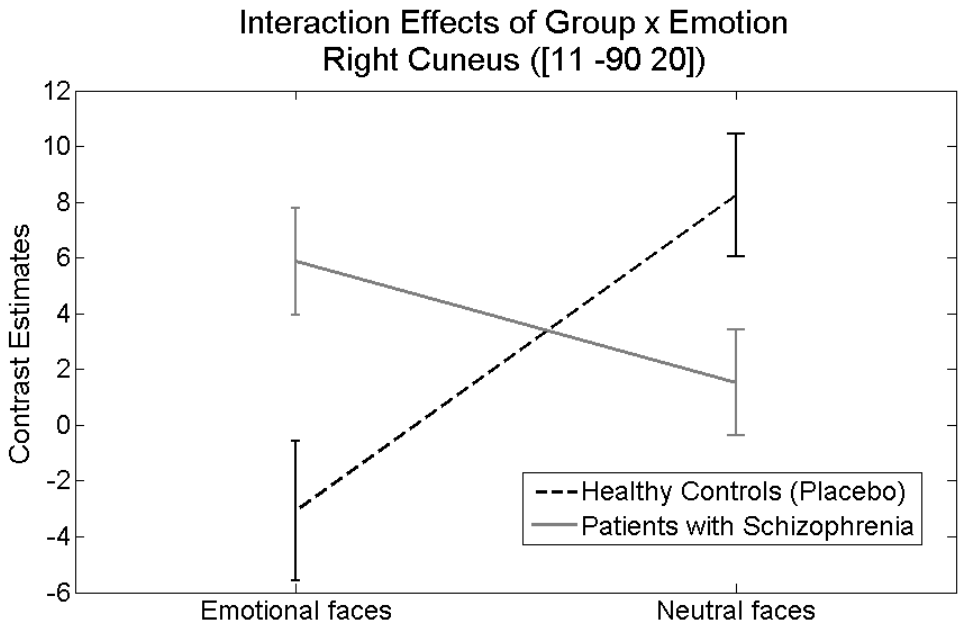

FIGURE 4.11 – Contrast estimates showing a significant interaction effect for neural activity between group and emotion within the peak voxel within the right cuneus The right cuneus was chosen for further analysis as this represented the peak voxel showing differences in neural activity during this interaction analysis. In this region, patients with schizophrenia showed greater neural activity when deciding between two emotionally valenced faced which was attenuated when deciding between two neutral faces and healthy controls showed the opposite pattern of neural activity.

As the amygdala is an important region for emotional processing and decision-making, a region of interest (ROI) analysis using small volume correction (SVC) was performed within a mask for the left and right amygdala. There was a significant interaction effect between group and emotional condition in the right amygdala (x = 33, y = 2, z = -26), t(120) = 3.74, p = 0.005, k = 20, with p representing the significance at FWE peak level correction (Figure 4.12 and Figure 4.13).

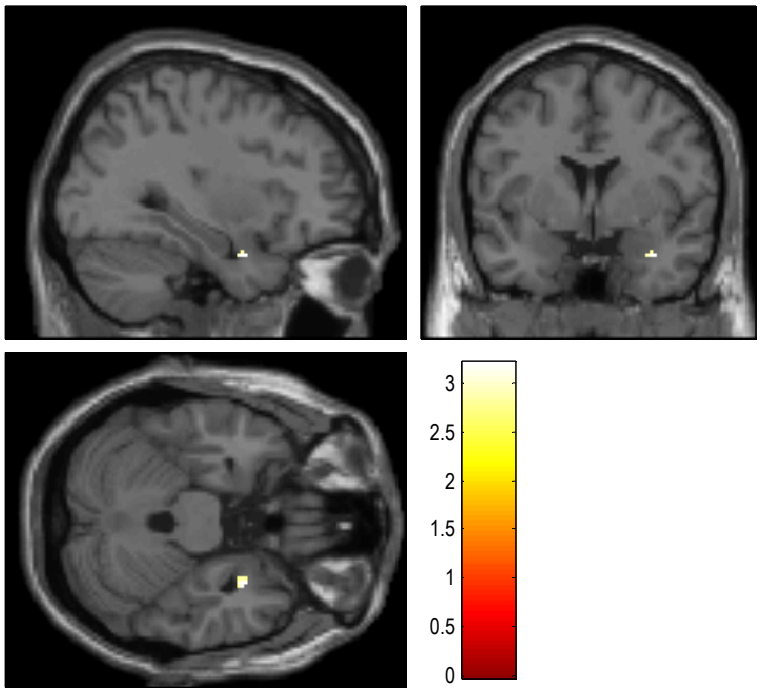

FIGURE 4.12 - Neural activity for interaction effects between group (patients with schizophrenia versus healthy controls on placebo) and emotion (emotionally valenced faces versus neutral faces) using SVC within the amygdala. Neural activity is greater in the healthy controls than the patients with schizophrenia in the right amygdala. This image is shown at an uncorrected height threshold of $p < 0.005$ with any peaks surviving FWE peak-level correction of $p < 0.05$ after SVC.

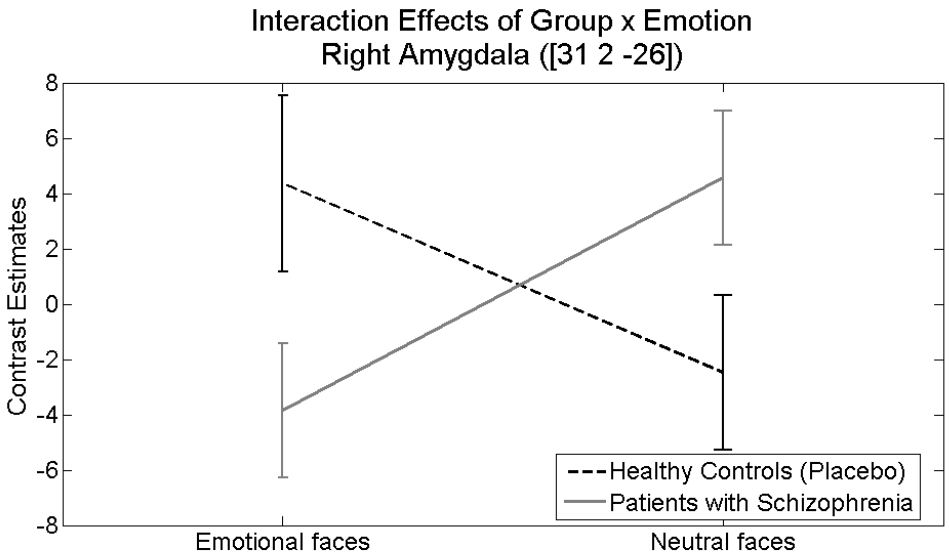

FIGURE 4.13 - Contrast estimates showing an interaction effect for neural activity between group and emotion in the right amygdala. This analysis reveals that patients with schizophrenia demonstrate attenuated levels of neural activity in the right amygdala when deciding between two emotionally valenced faces but show exaggerated levels of neural activity in this region when deciding between two neutral faces compared to healthy controls who have taken a placebo.

TABLE 4.4- Neural activity in patients with schizophrenia versus healthy controls on placebo when deciding between two faces

Group	Condition	Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
Healthy Controls (Placebo) > Patients with Schizophrenia	Decision (Emotional and Neutral faces)	R	Thalamus (MDN)*		5	-12	6	5.95	<.001	<.001	12103	1.64
		R	Thalamus (AN)*		13	-10	14	5.92	<.001	<.001	12103	1.63
		L	Thalamus*		-3	-22	6	5.21	<.001	<.001	12103	1.44
		L	Posterior Cingulate*	29	1	-38	22	5.26	<.001	<.001	12103	1.45
		R	Supramarginal Gyrus	40	59	-44	38	4.86	<.001	<.001	12103	1.34
		L	Cingulate Gyrus	23	1	-28	26	4.64	<.001	<.001	12103	1.28
		L	Cingulate Gyrus	23	3	-20	34	4.63	<.001	<.001	12103	1.28
		R	Cingulate Gyrus	24	23	-12	34	4.43	<.001	<.001	12103	1.22
		R	Cingulate Gyrus	31	9	-38	38	4.26	<.001	<.001	12103	1.18
		R	Cingulate Gyrus	31	5	-36	40	4.24	<.001	<.001	12103	1.17
		L	Anterior Cingulate	32	-15	30	12	4.53	<.001	<.001	12103	1.25
		R	Precuneus	7	5	-72	44	4.51	<.001	<.001	12103	1.25
		R	Precuneus	31	13	-64	34	4.09	<.001	<.001	12103	1.13
		R	Hippocampus		37	-44	8	4.01	<.001	<.001	12103	1.11
		L	Lingual Gyrus	18	1	-80	4	3.61	<.001	<.001	2112	1.00
		R	Lingual Gyrus	18	9	-80	2	3.33	0.001	<.001	2112	0.92
		L	Cerebellum (Culmen)*		1	-36	2	5.26	<.001	<.001	12103	1.45
		L	Cerebellum (Culmen)		-37	-56	-28	3.35	0.001	<.001	2112	0.93
		R	Cerebellum (Culmen)		45	-56	-26	4.00	<.001	<.001	2112	1.10
		L	Cerebellum (Declive)*		-15	-82	-20	5.90	<.001	<.001	2112	1.63
		R	Cerebellum (Declive)		11	-78	-18	4.79	<.001	<.001	2112	1.32
		R	Cerebellum (Declive)		41	-68	-20	3.84	<.001	<.001	2112	1.06
		R	Cerebellum (Declive of Vermis)		5	-80	-14	4.62	<.001	<.001	2112	1.28

Group	Condition	Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
		L	Cerebellum (Tuber)*		-33	-78	-30	5.01	<.001	<.001	2112	1.38
		L	Cerebellum (Tuber)		-43	-70	-28	4.50	<.001	<.001	2112	1.24
		L	Cerebellum (Uvula)		-39	-74	-24	4.30	<.001	<.001	2112	1.19
		R	Cerebellum (Uvula)		29	-72	-24	4.10	<.001	<.001	2112	1.13
		R	Cerebellum (Uvula)		25	-80	-24	3.91	<.001	<.001	2112	1.08
Patients with Schizophrenia > Healthy Controls (Placebo)	Decision (Emotional and Neutral faces)	R	Postcentral Gyrus	3	37	-28	52	4.73	<.001	0.004	1431	1.31
		R	Postcentral Gyrus	3	49	-16	50	4.41	<.001	0.004	1431	1.22
		R	Postcentral Gyrus	3	57	-8	44	4.25	<.001	0.004	1431	1.17
		R	Postcentral Gyrus	3	45	-24	52	4.17	<.001	0.004	1431	1.15
		R	Postcentral Gyrus	3	55	-12	48	4.14	<.001	0.004	1431	1.14
		R	Precentral Gyrus	4	35	-24	48	4.68	<.001	0.004	1431	1.29
		R	Precentral Gyrus	4	59	-4	38	4.28	<.001	0.004	1431	1.18
		R	Precentral Gyrus	4	57	-4	42	4.23	<.001	0.004	1431	1.17
		R	Precentral Gyrus	6	63	0	24	4.15	<.001	0.004	1431	1.15
		R	Precentral Gyrus	6	61	-2	34	4.04	<.001	0.004	1431	1.12
		R	Precentral Gyrus	4	65	-6	26	3.89	<.001	0.004	1431	1.07
Healthy Controls (Placebo) > Patients with Schizophrenia	Decision (Emotional faces)	R	Thalamus		7	-16	14	3.94	<.001	0.003	1374	1.09
		L	Thalamus		-5	-14	14	3.94	<.001	0.003	1374	1.09
		L	Thalamus		-5	-6	2	3.64	<.001	0.003	1374	1.01
		L	Thalamus		-3	-24	8	3.29	0.001	0.003	1374	0.91
		L	Thalamus (VLN)		-17	-8	4	3.30	0.001	0.003	1374	0.91
		L	Thalamus (VLN)		-13	-8	6	3.25	0.001	0.003	1374	0.90
		L	Putamen		-27	4	-2	3.21	0.001	0.003	1374	0.89

Group	Condition	Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
		L	Lateral Globus Pallidus		-19	-4	2	3.14	0.001	0.003	1374	0.87
		L	Cerebellum (Culmen)		1	-42	6	3.34	0.001	0.003	1374	0.92
Patients with Schizophrenia > Healthy Controls (Placebo)	Decision (Emotional faces)	R	Precentral Gyrus	6	63	-4	32	4.72	<.001	0.002	1461	1.30
		R	Postcentral Gyrus	3	47	-16	52	4.36	<.001	0.002	1461	1.20
		R	Postcentral Gyrus	3	37	-22	48	3.88	<.001	0.002	1461	1.07
		R	Postcentral Gyrus	3	35	-26	52	3.82	<.001	0.002	1461	1.05
		R	Precentral Gyrus	4	55	-6	46	3.71	<.001	0.002	1461	1.02
		R	Postcentral Gyrus	3	57	-12	38	3.66	<.001	0.002	1461	1.01
		R	Postcentral Gyrus	40	37	-30	60	3.59	<.001	0.002	1461	0.99
		R	Precentral Gyrus	4	43	-12	36	3.42	0.001	0.002	1461	0.94
Healthy Controls (Placebo) > Patients with Schizophrenia	Decision (Neutral faces)	L	Posterior Cingulate*	23	-1	-36	22	6.72	<.001	<.001	19617	1.86
		R	Thalamus (MDN)*		5	-12	6	6.60	<.001	<.001	19617	1.82
		R	Thalamus (AN)*		13	-8	14	6.36	<.001	<.001	19617	1.76
		L	Thalamus (MDN)*		-5	-10	6	6.19	<.001	<.001	19617	1.71
		L	Thalamus*		-3	-20	6	5.80	<.001	<.001	19617	1.60
		L	Thalamus (VLN)*		-17	-16	16	5.36	<.001	<.001	19617	1.48
		R	Precuneus*	31	15	-62	30	5.39	<.001	<.001	19617	1.49
		L	Lingual Gyrus*	18	1	-80	2	5.35	<.001	<.001	19617	1.48
		R	Middle Frontal Gyrus*	9	53	22	28	4.98	<.001	<.001	19617	1.38
		L	Cerebellum (Declive)*		-19	-80	-22	6.58	<.001	<.001	19617	1.82
		R	Cerebellum (Declive)*		13	-76	-18	5.86	<.001	<.001	19617	1.62
		R	Cerebellum (Declive)*		29	-70	-22	5.86	<.001	<.001	19617	1.62
		L	Cerebellum (Tuber)*		-35	-76	-30	6.16	<.001	<.001	19617	1.70

Group	Condition	Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
		L	Cerebellum (Tuber)*		-41	-72	-28	5.57	<.001	<.001	19617	1.54
		R	Cerebellum (Culmen)*		3	-36	2	5.25	<.001	<.001	19617	1.45
Group x Emotion Interaction		R	Cuneus	18	11	-90	20	4.54	<.001	0.046	682	1.25
		R	Cuneus	17	5	-78	18	3.35	0.001	0.046	682	0.93
		R	Cuneus	30	5	-76	14	3.32	0.001	0.046	682	0.92
		L	Middle Occipital Gyrus	18	-13	-90	20	4.42	<.001	0.046	682	1.22
		L	Middle Occipital Gyrus	19	-31	-80	30	3.85	<.001	0.046	682	1.06
		L	Middle Occipital Gyrus	19	-27	-90	20	3.01	0.002	0.046	682	0.83
		L	Lingual Gyrus	18	-7	-72	10	3.33	0.001	0.046	682	0.92
		L	Lingual Gyrus	18	-11	-80	10	3.04	0.001	0.046	682	0.84
		R	Amygdala[a]		33	2	-26	3.74	<.001	0.005[a]	20	1.03

Corresponding coordinates for each brain region listed represent the peak voxels for each corresponding region within each significant cluster. All areas reported were found to be significant at a family wise error cluster level corrected threshold of <.05 after running a whole brain analysis at an uncorrected threshold of p<.005. *p < .05 FWE peak level correction; k = cluster size BA = Brodmann's Area

a Regions which were found to be significant using small volume correction. FWE values are reported at peak level significance after correction

Effect size is calculated using Cohen's d

4.3.2.2 HEALTHY CONTROLS VERSUS PATIENTS WITH SCHIZOPHRENIA FOR REWARD PREDICTION ERROR (RPE)

When looking at the differences in neural activity correlating with reward prediction error when receiving feedback about their decision for both emotionally valenced and neutral faces no whole brain differences are observed between patients with schizophrenia and healthy controls. However, given that the ventral striatum has been a region previously shown to be activated by RPE, small volume correction was performed around this region. Patients with schizophrenia demonstrated greater bilateral neural activation in the putamen than healthy controls (peak coordinates: (x = -13, y = 6 z = -6), t(60) = 4.04, p = 0.004, k =14, (x = 13, y = 12, z = -4), t(60) = 3.28, p = 0.029, k = 24, where p represents the significance at FWE peak level when using SVC around the ventral striatum) (Figure 4.14). Looking at contrast estimates within the peak coordinate with the greatest difference in neural activity showed that these differences were due to a significant increase in neural activity in patients with schizophrenia while healthy controls showed relatively no changes in neural activity (Figure 4.15).

No interaction effects were found for differences in neural activity from group (patients with schizophrenia versus healthy controls who have taken a placebo) by emotion (emotionally valenced versus neutral faces), even when applying SVC in the ventral striatum, suggesting that these differences in neural activity are a general effect of RPE across conditions and not specific to processing emotionally valenced or neutral faces.

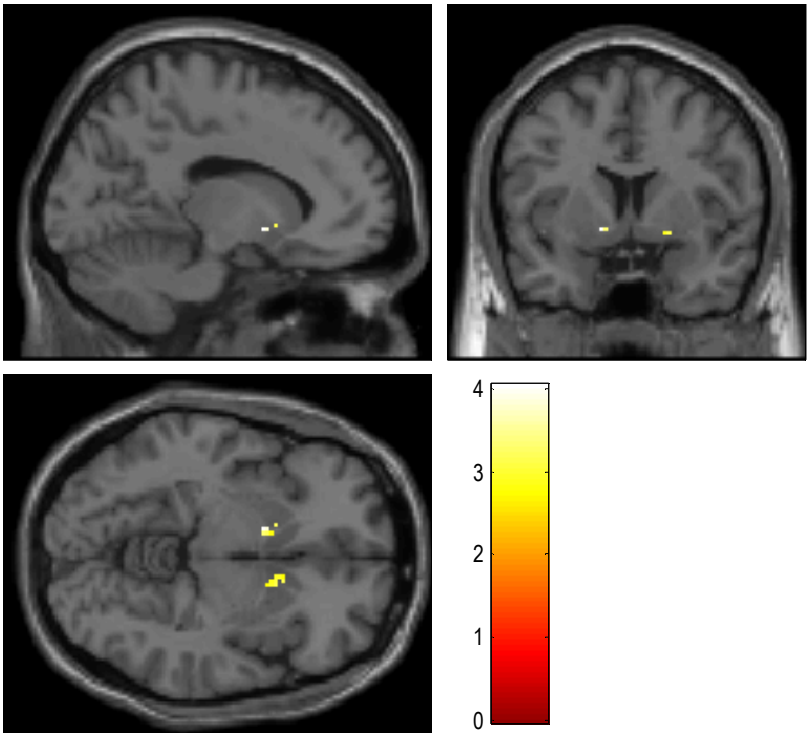

FIGURE 4.14 – Neural activity within a region of interest analysis around the ventral striatum for reward prediction error showing greater neural activity within the patients with schizophrenia in the bilateral ventral striatum compared to healthy controls.

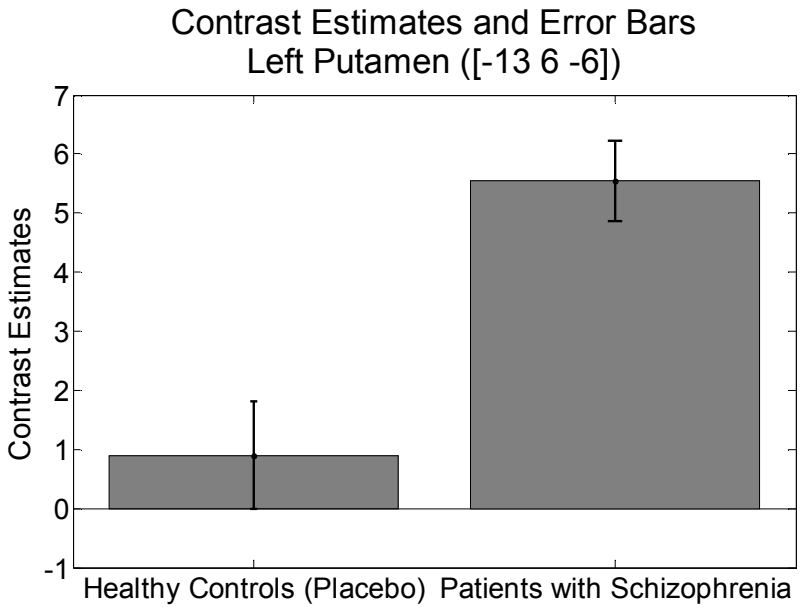

FIGURE 4.15 - Contrast estimates and 90% confidence intervals for RPE in the peak coordinate in the ventral striatum for healthy controls on placebo and patients with schizophrenia across both emotionally valenced and neutral faces. This shows that patients with schizophrenia have greater neural activation in the ventral striatum while healthy controls do not show much change in neural activation within this region.

4.3.2.3 GROUP DIFFERENCES IN NEURAL ACTIVITY DURING DECISION-MAKING USING SMALL VOLUME CORRECTION FROM AREAS AFFECTED BY DOPAMINERGIC PERTURBATION

To assess whether group differences in neural activity between patients with schizophrenia and healthy controls were reflective of changes in neural activity observed after dopaminergic perturbation in healthy participants, masks were taken from regions showing changes in neural activity from Chapter 3 and were used to assess if between group differences in neural activity existed after small volume correction (SVC).

4.3.2.3.1 DIFFERENCE TO ROPINIROLE INCREASES IN NEURAL ACTIVITY IN THE DACC/DMPFC IN HEALTHY CONTROLS WHEN DECIDING BETWEEN TWO EMOTIONALLY VALENCED FACES

When using an SVC analysis in the contrast between healthy controls and patients with schizophrenia during decision-making between two emotional faces taken from the same contrast between ropinirole and placebo administration in healthy participants found in Chapter 3 (page 79), no differences were observed in neural activity. Thus patients with schizophrenia do not show similar or opposing patterns of neural activity perturbation as healthy controls who have been administered ropinirole.

4.3.2.3.2 DIFFERENCE TO AMISULPRIDE DECREASES IN THE CEREBELLUM/ FUSIFORM GYRUS IN THE HEALTHY CONTROLS WHEN DECIDING BETWEEN TWO NEUTRAL FACES

When using an SVC analysis in the contrast between healthy controls and patients with schizophrenia during decision-making between two neutral faces taken from the same contrast but between amisulpride and placebo administration in healthy participants found in Chapter 3 (page 84), significant differences in neural activity were observed in the same regions seen in Chapter 3, within the right cerebellum

extending through the tentorium into the lingual and fusiform gyrus. Thus patients with schizophrenia appear to show similar patterns of attenuation in neural activity as healthy controls who have been administered amisulpride.

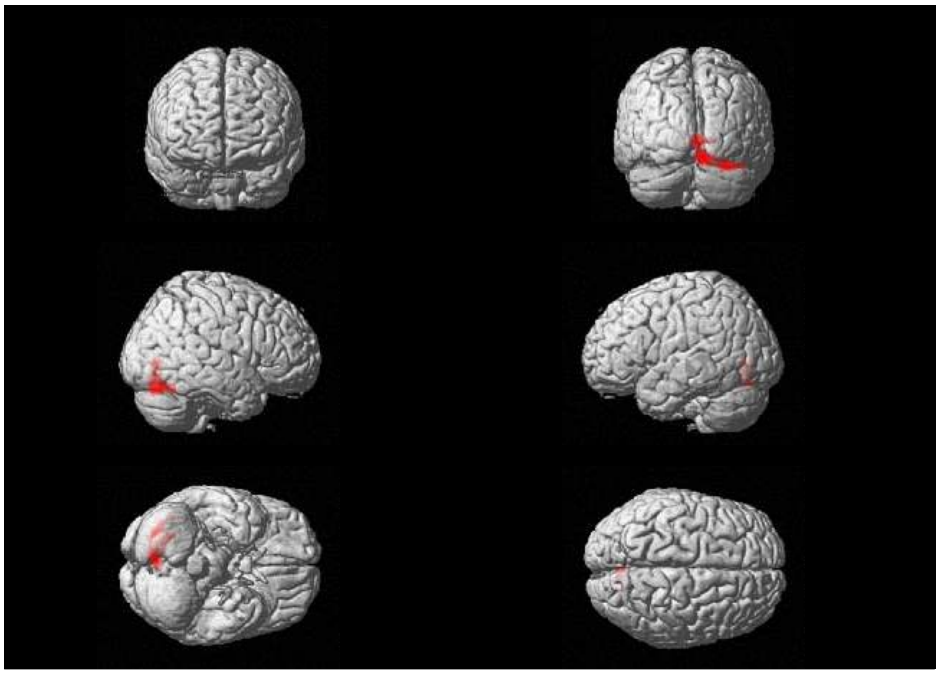

FIGURE 4.16 - Neural activity between healthy controls and patients with schizophrenia within a mask taken from between healthy particpants who have taken a placebo versus those who have taken amisulpride. Results are shown at a height threshold of $p<.005$ with an extent threshold of k = 100. As SVC was performed within this region, only voxels which survive FWE correction are shown.

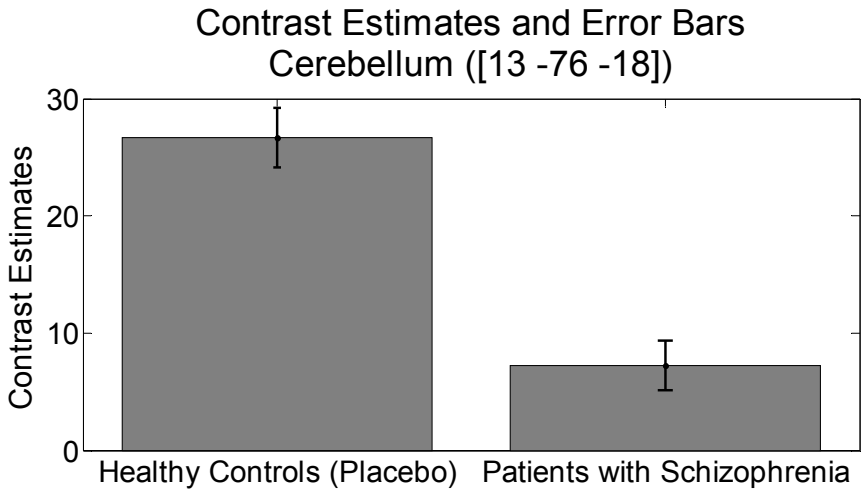

FIGURE 4.17 - Contrast estimates and standard error bars for neural activity within the cerebellum showing that neural activity is greater in the healthy controls than the patients with schizophrenia within the same region that shows an attenuation by amisulpride in healthy participants.

4.3.2.4 EFFECTS OF DOPAMINERGIC PERTURBATION ON NEURAL ACTIVITY DURING DECISION-MAKING IN HEALTHY CONTROLS USING SMALL VOLUME CORRECTION FROM BETWEEN GROUP DIFFERENCES

To assess whether group differences in neural activity between patients with schizophrenia and healthy controls were reflected in differences between healthy participants after dopaminergic perturbation, masks were created around regions which showed significant differences between patients with schizophrenia and healthy controls and were applied to a within group analysis in healthy controls after dopaminergic perturbation using SVC.

4.3.2.4.1 DIFFERENCES WITHIN THE REGIONS FOUND TO SHOW ABERRANT NEURAL ACTIVITY IN PATIENTS WITH SCHIZOPHRENIA

4.3.2.4.1.1 AMISULPRIDE VERSUS PLACEBO

When looking at differences in neural activity in healthy controls within the mask created for clusters which showed a significant difference in neural activity between patients with schizophrenia and healthy controls during decision-making in the combined emotionally valenced and neutral condition, no differences were found in healthy controls between the amisulpride and placebo condition.

No differences in neural activity were observed for the differences for decision-making in the emotionally valenced face condition either. However, when looking at differences within healthy controls taken from a mask around changes observed during decision-making between two neutral faces between the healthy controls and patients with schizophrenia, an attenuation of neural activity by amisulpride was observed in the left ACC (x = -17, y = 32, z = 14, t(19) = 5.60, p = 0.041 FWE peak level corrected) and a cluster in the precuneus (peak voxel, x = 3, y = -68, z = 48, t(19) = 3.49, p = 0.037, k = 471 FWE cluster level corrected). Interestingly,

although the right cerebellum and fusiform gyrus showed up within the mask, this cluster extending through the tentorium was only significant at a trend level (p = 0.063, k = 395).

4.3.2.4.1.2 ROPINIROLE VERSUS PLACEBO

No significant differences in neural activity were found within the masks taken from the group contrasts between healthy controls and patients with schizophrenia for any of the conditions looking at decision-making between emotionally valenced and neutral faces, both combined and separately, when using SVC between ropinirole and placebo.

4.4 DISCUSSION

This chapter explored the effect of dopaminergic manipulation on decision-making in an associative learning task in patients with schizophrenia using emotionally valenced and neutral faces as social variables. As hypothesised, patients with schizophrenia demonstrated the same bias toward choosing the happy face even when evidence supported the angry face as the better option. This bias in decision-making between two emotionally valenced faces was also accompanied by a change in neural activity within the bilateral thalamus, an area mainly known for relaying information between subcortical areas the cerebral cortex but which also aids in the planning and processing of decision-making by filtering and forwarding information (Buchsbaum et al., 2006; Haber and Calzavara, 2009). Furthermore, when looking at the general effect of decision-making across both emotionally valenced and neutral faces, attenuation of neural activity within the patients with schizophrenia was found to be the greatest in the medial dorsal nucleus (MDN) of the thalamus – a region known to be abnormal in patients with schizophrenia

(Andrews et al., 2006; Byne et al., 2001; Chana et al., 2008; Mitelman et al., 2005; Pakkenberg, 1990) – and extended to a further network including the cerebellum, a region involved in coordinating and connecting information, and processing social information and also known to show decreased neural activity in patients with schizophrenia (Andreasen and Pierson, 2008; Van Overwalle et al., 2014), and the dACC and mPFC, regions involved in decision-making through interpreting information and initiating responses (Asplund et al., 2010; Botvinick, 2007; Maier et al., 2012). When looking at similarities in the changes in neural activity between patients with schizophrenia and healthy controls and previous changes demonstrated by dopaminergic perturbation within healthy participants, patients with schizophrenia only showed similar patterns in neural activity to healthy controls who had received amisulpride compared to healthy controls who had taken a placebo. These changes in neural activity were apparent in the cerebellum and fusiform gyrus when both groups were deciding which face had a higher probability of being rewarded between two neutral faces. Conversely, when only looking at differences in the healthy participants within the networks listed above which showed differences in neural activity between patients with schizophrenia and healthy controls, similarities were only found for healthy participants who had taken amisulpride compared to a placebo when looking at neural activity when deciding between two neutral faces in the left ACC and right precuneus, also regions involved in decision-making (Botvinick, 2007; Cavanna and Trimble, 2006; Paulus et al., 2002). Together, these findings demonstrate that patients with schizophrenia show attenuated neural activity during this task within regions of the brain involved in the integration and coordination of decision-making. Although

these deficits were not all found to coincide with dopaminergic perturbation, they indicate that despite being able to perform the task with a similar degree of accuracy as healthy controls, patients with schizophrenia demonstrate a systematic deficiency in areas which are involved in integrating and coordinating information to form decisions.

When looking at differences in neural activity during decision-making, the strongest finding between groups was a significant attenuation in neural activity in the patients with schizophrenia in the thalamus compared to the healthy controls. The thalamus is known for being an area of integration where information is relayed between subcortical areas and the cerebral cortex and plays an important role in mediating motivation and emotional drive, as well as in planning and cognitive processes that guide decision-making (Buchsbaum et al., 2006; Haber and Calzavara, 2009). It is well connected to extensive regions of the frontal cortex which are involved in the formation of preference as well as planning and cognition (Cummings, 1993); the basal ganglia, which play a large role in processing reward information (Smith et al., 2004) and also the limbic system, including the amygdala, which helps processing emotional stimuli (Taber et al., 2004). The thalamus is subdivided into several specific regions with unique sets of afferent and efferent projections. One of these subdivisions, the MDN, an area known to be abnormal in patients with schizophrenia (Andrews et al., 2006; Byne et al., 2001; Chana et al., 2008; Pakkenberg, 1990) was found to be significantly attenuated in patients with schizophrenia compared to healthy controls in this study. Other studies looking at the size of the MDN in patients with schizophrenia have found an overall reduction

in volume and number of neurons in the MDN compared to healthy controls (Byne et al., 2001; Chana et al., 2008; Pakkenberg, 1990). Studies have also found a metabolic disconnection between the MDN and left lateralised fronto-temporal regions in patients with schizophrenia compared to healthy controls (Mitelman et al., 2005) which demonstrates that this area exhibits both structural and functional deficits in schizophrenia. One theory for the role of the thalamus in schizophrenia postulates that a defect in circuitry between the thalamus, frontal cortex and cerebellum accounts for how certain symptoms arise and is known as "cognitive dysmetria," or poor mental coordination (Andreasen, 1997; Andreasen et al., 1996; Andreasen et al., 1998). In a functioning network, the thalamus should act to filter and forward on stimuli while the cerebellum should coordinate and connect information and the frontal cortex should interpret information and initiate responses, however, deficits within this network in patients with schizophrenia are believed to undermine these functions. The attenuated neural activity within this network in our study further supports this model of cognitive dysmetria.

Further to these findings in the thalamus, and in further support of a deficit within this circuit, patients with schizophrenia showed a pattern of attenuated neural activity in the cerebellum compared to healthy controls after taking a placebo. Interestingly, this effect was also found in the cerebellum extending through the tentorium into the fusiform gyrus when looking at the effects of dopaminergic perturbation via amisulpride; healthy controls showed attenuated neural activity within this region after taking amisulpride compared to taking a placebo when deciding which face had a higher probability of being rewarded between two

neutral faces. This suggests that, at least within the cerebellum, some of these changes in neural activity observed in patients with schizophrenia may be driven by dopaminergic antagonists.

Although the cerebellum is mainly thought of as an area which is primarily dedication to the coordination of motor activity, recent evidence has emerged demonstrating the cerebellum's role in cognition and social processing as well as suggesting that its functioning is impaired in schizophrenia (Andreasen and Pierson, 2008; Van Overwalle et al., 2014). Furthermore, there is also evidence that some dopamine binding occurs in the cerebellum which can be influenced by antipsychotics (Hurley et al., 2003; Melchitzky and Lewis, 2000; Narendran et al., 2011). As both patients with schizophrenia and healthy controls who have received amisulpride showed attenuated neural activity in this area when deciding between two neutral faces, this suggests a tentative role for aberrant dopamine in the disruption of the coordination of information processing during this task in the cerebellum.

As all three areas of this purported network, the thalamus, cerebellum and mPFC were found to be attenuated in patients with schizophrenia, these findings appear to support aberrant processing within this network in patients with schizophrenia. Overall, studies support that there exist both structural and functional abnormalities with the thalamus in patients with schizophrenia which affects neural processing most likely by disrupting the integration of information is receives in conjunction with the cerebellum and mPFC. This study showed that patients with schizophrenia functionally mirror these deficits through attenuation of neural

activity when deciding which face they believe has a higher probability of winning. Even though this attenuation did not translate into significant deficits behaviourally, this showed that patients with schizophrenia do not recruit the same networks to the same degree as healthy controls. Furthermore, the lack of significant differences in neural activity within all of these regions in healthy controls after dopaminergic perturbation points to these deficits extending beyond dopaminergic differences in patients with schizophrenia but with some potential ties to dopaminergic aberrance in the cerebellum.

Further to this point, although this study did not explicitly measure connectivity, previous studies have shown dysconnectivity in patients with schizophrenia in the network presented here of the thalamus, cerebellum and mPFC, which provides some evidence that these areas are not communicating with each other as efficiently in healthy controls (Andreasen et al., 1996; Andreasen et al., 1998; Wiser et al., 1998). Regarding possible pathophysiological mechanisms underlying schizophrenia, the "dysconnection" hypothesis has garnered a significant amount of interest (Friston, 1998; Pettersson-Yeo et al., 2011; Stephan et al., 2006; Stephan et al., 2009). The principal behind this model is that the symptoms of schizophrenia arise due to aberrant effective connectivity between neural systems, or the influence that one system has over another (Kiebel et al., 2008), due to abnormal synaptic efficacy from neuromodulatory transmitters such as dopamine and glutamate (Stephan et al., 2009). It is also important to note that dysconnectivity is an overarching term for aberrant connectivity and does not only refer to diminished connectivity between regions but also to hyperconnectivity between regions.

Ineffective communication from one neural area to another is thought to be responsible for the emergence of symptoms such as the perception of internally generated speech as a voice from a separate entity and is evident even in tasks as simple as a visual attention task requiring no decisions (Roiser et al., 2013). Given that the regions in which patients with schizophrenia demonstrate the greatest attenuation of neural activity in this study are known to be regions highly interconnected regions within the brain, it is likely that these deficits in neural activity have arisen due to dysconnectivity between these regions. However, further exploration of these findings in regard to their functional connectivity will be necessary to confirm this theory.

Additionally, a region of interest analysis when looking at decision-making between two emotionally valenced faces versus two neutral faces between groups within the amygdala showed an interaction effect between healthy controls and patients with schizophrenia when deciding between emotional and neutral faces where healthy controls taking placebo recruited the amygdala more in the emotional condition than patients with schizophrenia and patients with schizophrenia showed greater activation of the right amygdala when deciding between neutral faces. However, differences in amygdalar activity were only apparent in an interaction analysis suggesting that within each condition, for emotionally valenced and neutral faces, patients with schizophrenia do not demonstrate aberrant levels of neural activity; however, they do appear to attribute aberrant patterns of neural activity to each of these conditions in comparison to healthy controls.

Unexpectedly, when looking at the association between neural activity and RPE, patients with schizophrenia showed greater bilateral neural activity in the striatum than healthy controls who had taken a placebo. This finding is surprising in light of the few current studies which have shown relative decreases in RPE in patients with schizophrenia compared to healthy controls (Gradin et al., 2011; Murray et al., 2008; Rausch et al., 2014). However, it is also important to note that these studies did still find systematic increases in neural activity within the striatum in patients with schizophrenia, albeit to a lower extent than healthy controls. Furthermore, one study even found that when only looking at the effects of expected reward, patients with schizophrenia showed elevated neural activity in the ventral striatum compared to healthy controls (Morris et al., 2012). Chapter 3 provided surprising results as well showing that healthy controls did not display the robust increase in neural activity in the striatum correlating with RPE as expected. As the model adapted for this study was designed to be simplistic in its nature, it is possible that this model tracked neural activity in patients with schizophrenia with greater accuracy than healthy controls or the reward stimuli used in this study had a greater effect on patients with schizophrenia than healthy controls. As explored in Chapter 3 (page 56), studies looking at RPE and dopamine have not always provided consistent results in terms of increased or decreased neural activity as a result of dopaminergic perturbation (Jocham et al., 2011; Murray et al., 2008; Pessiglione et al., 2006). Therefore it is not entirely surprising that this study also found different effects for RPE than previously observed in patients with schizophrenia.

Overall, these findings suggest that patients with schizophrenia show differential patterns of neural activity in areas of connectivity such as the thalamus and cerebellum indicative of “cognitive dysmetria” or dysconnectivity within this group. Although these findings did not all coincide with changes in neural activity observed after dopaminergic perturbation, patients with schizophrenia do show some similar patterns in neural activity particularly within the cerebellum and fusiform gyrus to healthy controls who have taken amisulpride suggesting that this region may be influenced by dopaminergic antagonist medication.

CHAPTER 5 - NEUROPYHSIOLOGICAL EFFECTS OF ACUTE OXYTOCIN ADMINISTRATION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PLACEBO-CONTROLLED IMAGING STUDIES

5.1 INTRODUCTION

The role of oxytocin in influencing social behaviour has been well established in animal research(Insel and Young, 2001a; McCall and Singer, 2012) but over the past decade has been increasingly shown to be relevant in humans(Meyer-Lindenberg et al., 2011). Early research focussed on its core role in parturition, milk ejection, sexual function and parenting but recent studies have focussed on its effects on social behaviour(Insel and Young, 2001a). The use of evolving technologies in animal models such as oxytocin receptor agonists and antagonists, receptor knockouts and autoradiography have all helped to identify analogous areas of interest for examination in human research(McCall and Singer, 2012; Neumann and Landgraf, 2008) and have contributed the basis of further investigation of the effects of OXT on human behaviour and social cognition (Gimpl and Fahrenholz, 2001).

In behavioural studies oxytocin has been linked to social behaviours such as trust and parental bonding. It has also been shown to increase the ability to identify emotions, increase empathy toward others, and attenuate aversion to angry faces (Bartz et al., 2011; McCall and Singer, 2012). Furthermore, its role in facilitating social interactions by ameliorating social bias and response to emotional faces has led it to be considered as a possible drug to use in disorders with severe social deficits such as autism and schizophrenia (Evans et al., 2010; Guastella and MacLeod, 2012).

The neurophysiological effects of oxytocin were initially investigated in animal models before testing in humans. Although oxytocin is produced and secreted in the same areas in both humans and animals, the receptor distribution can vary in a species specific manner (Gimpl and Fahrenholz, 2001; Loup et al., 1991). Much of this variation may be due to species specific differences in the way social stimuli are perceived and processed - with subsequent reorganisation of neural connections in favour of more developed areas in each species. For example, in rats, the primary source of social input is through odour, whereas in humans it is based on visual and auditory cues, and relies heavily on facial cues(McCall and Singer, 2012). oxytocin is synthesised in the hypothalamic paraventricular parvocellular neurons (PVN) and the supraoptic nuclei (SON) and is then secreted by the posterior pituitary. Neurons from the PVN project to various areas in the limbic system (hippocampus, amygdala, striatum, hypothalamus and nucleus accumbens) which are involved in social cognition (Gimpl and Fahrenholz, 2001). With this in mind, recent neuroimaging techniques have allowed scientists to investigate in vivo the neurophysiological correlates of the effect of oxytocin. By examining fluctuations in the hemodynamic activity in the brain using functional magnetic resonance imaging (fMRI) after the administration of oxytocin compared to the administration of a placebo, the network and regions that contribute to oxytocin's influence over brain activity have become clearer.

This systematic review and meta-analysis aims to provide an integrative and comprehensive review of placebo-controlled neuroimaging studies of oxytocin. We will also report the magnitude of change in activation of various brain regions as a result of oxytocin administration versus a placebo during tasks related to social behaviour by computing its effect sizes in the limbic system – including the amygdala -, the reward

system, the frontal lobe, and the temporal lobe. Finally, we will look at a voxel-based meta-analysis of the effect of oxytocin administration on the human brain as addressed by various fMRI studies. An examination of animal studies has also been performed and is presented in the Supplementary Materials of the published paper but will not be presented in this thesis (Wigton et al., in press).

5.2 METHODS

5.2.1 SEARCH STRATEGIES

A systematic search strategy following the PRISMA guidelines for systematic reviews (Liberati et al., 2009) was used to identify relevant studies for this review. Initially, the search used Embase, Medline and PsychInfo to identify relevant studies (published from 1806 up to 7 February 2013). To be included, each study had to be an original study using oxytocin as a pharmacological manipulator of brain activity. Since this review aims to cover all types of brain imaging, search parameters were expanded to include different brain imaging techniques. Search terms included “oxytocin”, “magnetic resonance imaging,” “MRI”, “fMRI”, “magnetoencephalography”, “MEG”, “electroencephalography”, “EEG”, “positron emission tomography”, “PET.”

The bibliographies in the retrieved articles were also hand searched to uncover relevant papers that may have been missed in the search. Although no limits were placed on the language for an article, all articles found that fit our selection criteria were in English. No articles were found for MEG or PET research using oxytocin as a pharmacological probe. Studies were only included if they were an original publication in a peer-reviewed journal.

5.2.2 SELECTION CRITERIA

We included only studies that fit all of the following criteria: (i) explored the effects of intranasal administration of oxytocin in a placebo-controlled double-blind design, (ii) used functional neuroimaging or electrophysiological techniques. Studies which used a patient population but also reported findings for healthy controls were included if they satisfied all other criteria. Exclusion criteria were post-mortem studies, structural imaging techniques, studies only looking at endogenous oxytocin and studies on vasopressin or oxytocin antagonists as these studies did not look at how oxytocin administration affected brain activity. Only intranasal administration in humans was explored as this is the most common method of administering oxytocin in current imaging studies and there is a body of research supporting its influence over brain regions by potentially increasing its concentration in the CSF (Born et al., 2002; van Ijzendoorn et al., 2012).

For the whole brain fMRI voxel-based meta-analysis, further criteria were applied. Only studies using emotional stimuli in healthy controls and that reported the peak coordinates of homogenously-thresholded oxytocin effects at the whole-brain level were included as there were not enough studies using social interactions alone to allow for an additional comparison. A total of 11 studies fit all the criteria and were included in the meta-analysis (Figure 5.1).

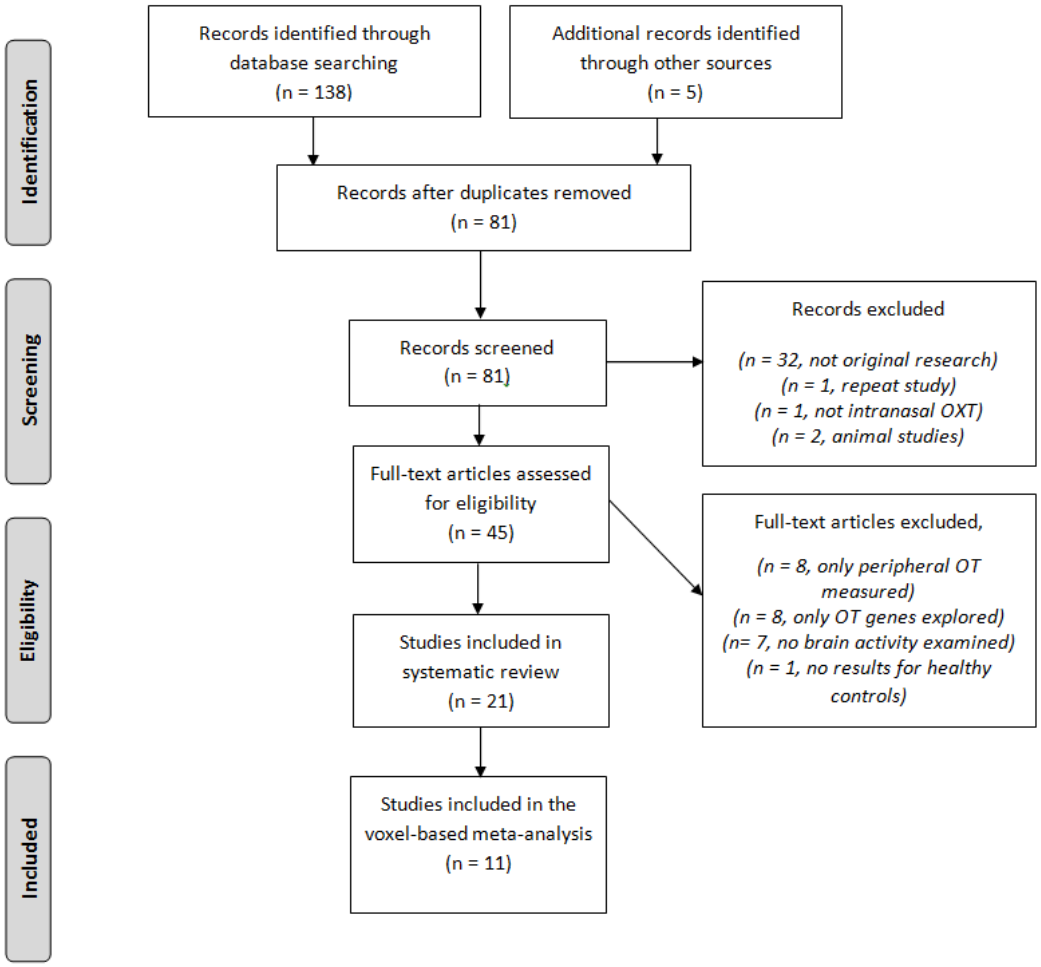

FIGURE 5.1 - PRISMA flow diagram for all human studies included in the review

5.2.3 SYSTEMATIC REVIEW

For each retrieved study we recorded the following variables: number of subjects, study design, gender, dosage of oxytocin, the tasks implemented, major findings, areas attenuated or activated by oxytocin administration and their corresponding coordinates, contrasts and statistical value.

Results were comprehensively reported in tables to assist the reader in forming an independent view on the following discussion. In particular, we decided to discuss the core findings with respect to different brain areas of interest: Basal ganglia, Insula,

Thalamus, Temporal lobes, Prefrontal cortex (PFC) and Amygdala as these are the areas most commonly reported in studies using oxytocin.

5.2.4 EFFECT SIZES

We analysed the magnitude of the oxytocin effects (effect sizes) on the regions of interest outlined in Table 5.3. Where sufficient information was provided in a study to assess the significance of the results (eg presence t value, p-value, F value, or means and standard deviations), we calculated the effect size.

Studies which fit the criteria for effect size analysis accounted for 11 of the 15 studies reporting modulation from oxytocin aside from connectivity measures. The effect size is a dimensionless number which facilitates the integration of findings across studies that used different types of measurements. The choice of effect size estimator is a much debated and still unresolved issue (Hunter and Schmidt, 1990) and is related to the choice of whether or not greater reliance should be laid on studies carried out on larger samples when the effect size is to be computed. We chose to use an effect size estimator corrected for the number of subjects included in each study using Cohen's d statistic (Cohen, 1992) generated by the SPSS program. We calculated these values because most studies included fairly small numbers of subjects. When the power of a study is insufficient to show statistically significant differences between or within groups, even when such is the case in the population, type II errors occur. By examining effect sizes rather than statistical significance, we can better understand what differences exist in the general population and whether these differences might merit further study. Effect size (d) is taken to mean 'the degree to which a phenomenon is present in the population' (Cohen, 1988, p. 9); we indexed d according to Cohen's scheme (Cohen, 1992). Cohen placed the value of d for small effects at 0.2,

for medium effects at 0.5, and for large effects at 0.8.

5.2.5 VOXEL-BASED META-ANALYSIS

Meta-analysis of the oxytocin effects at the whole-brain level was conducted with the effect-size version of Signed Differential Mapping (ES-SDM, http://www.sdmproject.com/) (Radua and Mataix-Cols, 2012; Radua et al., 2012b), a technique that has already been applied to the study of both healthy controls (Peters et al., 2012) and many neuropsychiatric disorders such as ADHD (Hart et al., 2013), anxiety (Radua et al., 2010), autism (Radua et al., 2011) and schizophrenia (Fusar-Poli et al., 2012; Radua et al., 2012a).

Briefly, ES-SDM used the information reported in the papers about the brain peaks of maximum oxytocin effects to recreate a statistical parametric map for each study, and then conducted a standard meta-analysis to obtain a meta-analytic brain map of oxytocin's effects. First, peak coordinates were converted to Talairach space and their t-values were converted into effect sizes and their standard errors – i.e. accounting for study precision and sample size. It must be noted that SDM software was modified in order to account for the fact that some of the studies had conducted one-sample tests while others had conducted two-sample tests. Second, each peak was used to recreate a cluster of voxels with significant oxytocin effects by assigning an effect-size to the voxels close to the peak, taking the distance of each voxel to the different close peaks into account. Finally, the different recreated maps were voxel-wise combined by fitting random-effects models and p-values were derived from a permutation test. Results were thresholded with voxel $p \leq 0.005$, peak $z \geq 2$, and cluster extent ≥ 10 voxels. Please see (Radua and Mataix-Cols, 2012) for further details.

This analysis was complemented with two other analyses to assess the robustness of the meta-analytic findings. First, we conducted a jack-knife test which consisted in repeating the meta-analysis many times, with each time including all the studies but one, in order to infer the replicability of the findings. Second, funnel plots were drawn from the meta-analytic peaks in order to discard publication bias and gross abnormalities. Potential publication biases were further assessed with Egger tests (Figure 5.2b).

5.3 RESULTS

5.3.1 DATABASE

Our literature search uncovered 21 full papers which met our inclusion criteria. Details of the retrieved studies are given in Table 5.1.

To make the anatomical labelling of the relevant areas reported more consistent, all coordinates from each study were converted to Talairach coordinates using icbm2tal for the appropriate template (i.e. SPM, FSL etc) (Lancaster et al., 2007b). These coordinates were then entered into Talairach client (Lancaster et al., 2000) to create a standardised list of areas reported by each study. When different to the areas reported by the study, this was noted as shown in Table 5.2 and is referenced throughout the systematic review.

In the studies, 16 used fMRI and 5 used EEG to explore the effects of oxytocin. The voxel based meta-analysis in fMRI studies included a total of 11 studies. Details of the literature search are described in the PRISMA flowchart in Figure 5.1

TABLE 5.1 - Overview of all imaging studies reviewed

Author, year	Sample size	within/ between	Gender	Technique	OXT dose	Task used	Brain areas analysed	Effects of oxytocin
Baumgartner et al, 2008	49	between	M	fMRI	24 IU	Trust game	Amygdala, Brainstem, Caudate, Putamen, Insula, Thalamus	Increased trust in partner after trust had been violated
Domes et al, 2007	13	within	M	fMRI	24 IU	Implicit facial emotion processing by identifying gender of fearful, angry and happy faces	Amygdala, Temporal Pole, TPJ, Thalamus, PFC	Increased ability to identify emotions
Domes et al, 2010	16	within	F	fMRI	24 IU	Explicit facial emotion processing by rating arousal of fearful, angry and happy faces	Amygdala, Brainstem, Temporal pole, Superior Temporal Gyrus, Fusiform gyrus, Insula, PFC, Thalamus	Greater arousal in rating facial emotions
Gamer et al, 2010	46	between	M	fMRI	24 IU	Explicit facial emotion processing by classifying emotion of fearful and happy faces	Amygdala, Superior Colliculus	Increased ability to identify emotions, gaze starts at mouth and is redirected to eyes for longer
Kirsch et al, 2005	15	within	M	fMRI	27 IU	Implicit facial emotion processing by matching fearful and angry faces	Amygdala, Brainstem	Increased ability to identify emotion
Labuschagne et al, 2010*†	18	within	M	fMRI	24 IU	Implicit facial processing by matching angry, fearful, happy and neutral faces	Amygdala	Insignificant decreases in amygdala activity
Labuschagne et al, 2012*	18	within	M	fMRI	24 IU	Explicit facial processing using emotional classification of sad, happy and neutral faces	mPFC, ACC, Thalamus, STG	General attenuation in areas associated with processing social stimuli, cognitive control, and emotion regulation
Lischke et al, 2012	14	within	F	fMRI	24 IU	Explicit processing by rating emotional arousal of negative, positive and neutral scenes	Amygdala, Temporal Pole, Fusiform gyrus	Increased threat-sensitivity in amygdala to scenes depicting social and non-social threat. No changes in eye-tracking

Author, year	Sample size	within/ between	Gender	Technique	OXT dose	Task used	Brain areas analysed	Effects of oxytocin
Petrovic et al, 2008	27	between	M	fMRI	32 IU	Aversely conditioned face processing by rating likeability of faces that were previously paired with a negative experience	Amygdala, Anterior cingulate, vlPFC, fusiform area	Increased likeability of faces even after being linked to aversive stimuli
Pincus et al, 2010**	9	within	1M/8F	fMRI	40 IU	Explicit emotional processing using Reading of the Mind's Eye Test (RMET) by emotional classification	Caudate, Amygdala, ACC, STG, GP	Oxytocin increased activity in areas associated with reward and processing of social stimuli
Riem et al, 2011	42	between	F	fMRI	24 IU	Auditory exposure to babies crying	Amygdala, Insula	decrease in amygdala to sound clips of crying babies
Riem et al, 2012	42	between	F	fMRI	16 IU‡	Auditory exposure to infant laughter	Connectivity between the Amygdala and the OFC, ACC, hippocampus, precuneus, supramarginal gyri and MTG	Increased functional connectivity between the amygdala and other areas involved in regulating emotion and decrease in amygdala when listening to laughter over control noise
Rilling et al, 2012	60	between	M	fMRI	24 IU	Altruistic interaction	Amygdala, Caudate, ventral PFC, Insula, Putamen	Differences in activity in reciprocated and unreciprocated cooperativity, increase in Amygdala only in reciprocated interaction
Singer et al, 2008	20	between	M	fMRI	32 IU	Empathy for pain and experience of pain	PFC, OFC, Amygdala	no significant observations in response to viewing their partner in pain, reduced amygdala activation when receiving painful stimulation
Sripada et al, 2012	15	within	M	fMRI	24 IU	Resting state connectivity	Amygdala to ACC/rmFC	Increased connectivity during resting state
Striepens et al, 2012	70	between	M	fMRI	24 IU	Implicit processing of social scenes using a memory task with negative and neutral pictures paired with nouns	Insula, Amygdala	Increased memory for negative pictures at the expense of neutral stimuli which was accompanied by an increase in the left insula and changes in connectivity between the insula and amygdala

Author, year	Sample size	within/ between	Gender	Technique	OXT dose	Task used	Brain areas analysed	Effects of oxytocin
Wittfoth-Schardt et al, 2012	21	within	M	fMRI	24 IU	Implicit facial processing of familiar and unfamiliar faces	Globus Pallidus, MTG, Caudate	Reduced activity and functional connectivity to the GP from reward related regions to pictures of own child and unknown child
Born et al, 1987	17	within	M	EEG	40 IU	Auditory mismatch paradigm	N2 and P3	no effect of oxytocin
Fehm-Wolfsdorf, 1988	30	between	M	EEG	20 IU	memory recall of 25 nouns, tone counting	auditory evoked potentials	no effect of oxytocin on memory or auditory stimuli
Huffmeijer et al, 2012	47	between	F	EEG	15.6 IU	Altruistic interaction	frontal asymmetry	increased donations from oxytocin corresponded with decrease in left/increase in right frontal activity
Huffmeijer et al, 2012	48	within	F	EEG	16 IU	combination of feedback processing and facial processing	vertex positive potential (VPP) and late positive potential (LPP)	more positive VPP and LPP after oxytocin which was heightened more for those experiencing less love withdrawal
Perry et al, 2010	24	within	M	EEG	24 IU	point-light experiment to mimic biological and non-biological motion	mu rhythms	better able to identify biological movement which corresponded to mu suppression across the whole scalp

nr = not reported; OXT = oxytocin; IU = International Units; M = male; F= female; ACC = Anterior cingulate cortex, PFC = Prefrontal cortex, mPFC = medial prefrontal cortex, vlPFC = ventro lateral prefrontal cortex, rmFC= rostro-medial frontal cortex GP = Globus pallidum, STG = superior temporal gyrus, TPJ = temporo-parietal junction, VTA = ventral tegmental area

sample size only incudes subjects used in the oxytocin and placebo samples. Other subjects may have also done the study under other arms

*also included 18 patients with generalised anxiety disorder but only results from healthy controls reported.

**also included patients with depression but only results from healthy controls are reported.

†Excluded from analysis other than that of the amygdala because no direction of effects were reported ‡ reported as 20 IU but later wrote an erratum to show that it was really 16 IU

5.3.2 SYSTEMATIC REVIEW

The present systematic review aims to elucidate the role/effect of oxytocin in various regions of the brain and their corresponding networks. The specific brain areas modulated by oxytocin in each study are detailed in Table 5.2 and further details on the differences between oxytocin receptors and its administration between humans and animals can be found in the Supplementary Materials which are presented in the published paper.

We have also assessed the magnitude of oxytocin effects by providing the Cohen's d for specific brain areas in the complementary Table 5.3.

TABLE 5.2 - Overview of direction of neural activity after oxytocin administration

Author, year	**Sample size**	**within/ between**	**Gender**	**Task *(contrast)***	**Effect of oxytocin**	**wb/ ROI**
Baumgartner et al., 2008	49	between	M	Trust interaction as trustee with human and risk interaction with a computer		
	23 placebo *26 oxytocin*			*Trust feedback*	↓L/R Amygdala	wb
					↓L Brainstem	wb
					↓L/R Caudate	wb
					↓L Postcentral gyrus *(Superior parietal lobe)*	wb
					↓L Putamen/Insula	wb
				Trust prefeedback	↑R Thalamus/pulvinar	wb
					↓R ACC	wb
Domes et al., 2007	13	within	M	Implicit facial processing by indicating gender of happy, angry, fearful and neutral faces *Implicit facial processing (fearful > neutral)*	↓L Paracentral gyrus	wb
					↓L Frontal medial lobe *(MFG)*	wb
					↓L Medulla	wb
					↓Anterior cerebellum/Culmen	wb
					↓L Inferior Temporal Lobe *(MTG)*	wb
					↓L MTG	wb

Author, year	Sample size	within/ between	Gender	Task *(contrast)*	Effect of oxytocin	wb/ ROI
				Implicit facial processing (angry > neutral)	↓L Thalamus/Pulvinar	wb
					↓L Postcentral gyrus *(paracentral lobe)*	wb
					↓R Precentral gyrus *(postcentral gyrus)*	wb
				Implicit facial processing (happy > neutral)	↓L/R Inferior Temporal Lobe *(STG)*	wb
					↓L Paracentral gyrus	wb
					↓L MTG	wb
Domes et al., 2010	16	within	F	Explicit facial processing by rating emotional arousal of fearful, angry, happy and neutral faces		
				Explicit facial processing (fearful > neutral)	↑L MTG (Temporal Pole)	wb
					↑L Amygdala *(subcallosal gyrus)*	wb
					↑L/R Fusiform Gyrus *(L cerebullum/ R parahippocampal gyrus)*	wb
					↑L STG	wb
					↑L Insula	wb
					↑R Cerebellum	wb
					↑R Brainstem *(SN)*	wb
					↓R dlPFC *(SFG)*	wb
				Explicit facial processing (angry > neutral)	↑L Rolandic operculum *(Insula)*	wb
					↑R Rolandic operculum *(Thalamus)*	wb
					↑R dlPFC *(MFG)*	wb
					↑L/R vlPFC *(MFG)*	wb
				Explicit facial processing (happy > neutral)	↑L MTG (Temporal Pole)	wb
					↑R Hippocampus *(Amygdala)*	wb
					↑L STG *(transverse temporal gyrus)*	wb
					↑L Fusiform gyrus *(cerebellum)*	wb
					↑L Insula *(postcentral gyrus)*	wb
					↑R Rolandic Operculum *(precentral gyrus)*	wb
					↑R Cerebellum	wb
					↓R dlPFC *(SFG)*	wb
Gamer et al., 2010	46	between	M	Explicit facial processing by emotional classification of fearful, happy, and neutral faces		
	23 placebo *23 oxytocin*			*Explicit facial processing (fearful > neutral)*	↓L/R Amygdala	ROI

Author, year	Sample size	within/ between	Gender	Task *(contrast)*	Effect of oxytocin	wb/ ROI
				Gazing toward eyes	↑R posterior Amygdala	ROI
				Gazing toward mouth	↑L/R Superior Colliculus *(cerebellum)*	wb
Kirsch et al., 2005	14	within	M	Implicit emotional processing by matching fearful/threatening scenes and angry/fearful faces or shapes *All social stimuli, but greater for faces*	↓L Amygdala	ROI
				Connectivity measures	↓L Amygdala-L/R Brainstem	ROI /ROI
Labuschagne et al., 2012**	18	within	M	Explicit facial processing using emotional classification of sad, happy and neutral faces *Explicit facial processing (sad > neutral)*	↓R ACC	wb
					↓R MFG	wb
					↓R Supplementary motor cortex *(MFG)*	wb
					↓L Superior parietal cortex *(precuneus)*	wb
					↑L Thalamus	wb
				Explicit facial processing (happy > neutral)	↓L Cerebellum	wb
					↓L Cerebellum/fusiform	wb
					↓L Calcarine fissure/cerebellum	wb
					↓R mPFC *(MFG)*	wb
					↓L MFG	wb
					↓L Precuneus *(cuneus)*	wb
					↑R STG *(IFG)*	wb
Lischke et al., 2012	14	within	F	Explicit processing by rating emotional arousal of negative, positive and neutral social scenes *Explicit social processing (negative > neutral scenes)*	↑L/R Amygdala *(/R Putamen)*	ROI
					↑L MTG	wb
					↑L inferior temporal gyrus *(fusiform gyrus)*	wb
					↑L temporal pole: STG	wb
					↑L postcentral gyrus	wb
				Explicit social processing (positive > neutral scenes)	↓R Supplementary motor cortex *(SFG)*	wb

Author, year	Sample size	within/ between	Gender	Task *(contrast)*	Effect of oxytocin	wb/ ROI
Petrovic et al., 2008	27 *12 placebo* *15 oxytocin*	between	M	Conditioned neutral faces with direct and indirect gaze to aversive stimuli (Implicit processing) *Fear conditioning (main effect)*	↓R anterior MTL *(MFG)*	ROI
					↓R vmPFC *(ACC)*	wb
					↓L lateral OFC *(IFG)*	wb
					↓R ACC	wb
					↓R rostral ACC *(MFG)*	wb
					↓L vlPFC *(IFG)*	wb
				Fear conditioning for direct gaze	↓R Amygdala *(subcallosal gyrus)*	ROI
					↓L/R caudal ACC	wb
					↓R subgenual ACC	wb
					↑L vlPFC *(MFG)*	wb
					↓R vlPFC *(MFG)*	wb
					↓R fusiform face area	wb
Pincus et al., 2010*	9	within	M/F (1M/8F)	Explicit facial processing using Reading of the Mind's Eye Test and emotional classification *All stimuli*	↑ L Caudate	wb
					↑R Parahippocampal gyrus	wb
					↑R Amygdala	wb
					↑R Inferior frontal gyrus *(MFG)*	wb
					↑L Lentiform nucleus *(GP)*	wb
					↑L Anterior cingulate	wb
					↑R Parahippocampal gyrus	wb
					↑L Caudate *(Parahippocampal gyrus)*	wb
					↑L STG *(MTG)*	wb
					↑L STG *(MTG)*	wb
					↑L ACC *(subcallosal gyrus)*	wb
					↑L ACC *(MFG)*	wb
Riem et al., 2011	42 *21 placebo* *21 oxytocin*	between	F	Auditory exposure to babies crying *Implicit emotional processing (Infant's cry > control noise)*	↓R Amygdala *(GP)*	ROI
					↑L Planum polare *(STG)*	wb
					↑R IFG *(Insula)*	wb
Riem et al, 2012	42 *20 placebo* *22 oxytocin*	between	F	Auditory exposure to infant laughter *Implicit emotional processing (Infant's laughter > control noise)*	↓L/R Amygdala	ROI

Author, year	Sample size	within/ between	Gender	Task *(contrast)*	Effect of oxytocin	wb/ ROI
				Connectivity (laughter > control noise)	↑R Amygdala - L Hippocampus	ROI /wb
					↑R Amygdala - L Precuneus	ROI /wb
					↑R Amygdala - R MTG	ROI /wb
					↑R Amygdala - R Parahippocampal gyrus	ROI /wb
					↑R Amygdala - L OFC	ROI /wb
					↑R Amygdala - L Angular gyrus	ROI /wb
					↑R Amygdala - L ACC	ROI /wb
					↓R Amygdala - R lateral occipital cortex	ROI /wb
					↑L Amygdala - ACC	ROI /wb
					↓L Amygdala - R lateral occipital cortex	ROI /wb
Rilling et al., 2012	60	between	M	Altruistic interaction using the prisoner's dilemma		
	34 placebo			*Reciprocated cooperation*	↑L Caudate *(parahippocampal gyrus)*	wb
	26 oxytocin				↑L Amygdala *(parahippocampal gyrus)*	wb
					↑R Putamen/Insula	wb
				Unreciprocated cooperation	↑L vlPFC *(MFG)*	wb
					↑L vmPFC *(MFG)*	wb
				Connectivity	↑R Amygdala - R MTG/STG	ROI /wb
					↑R Amygdala - R IFG	ROI /wb
					↑R Amygdala - L MFG/postcentral gyrus	ROI /wb
					↑R Amygdala - L anterior insula/IFG	ROI /wb
					↑R Amygdala - L planum polare/STG	ROI /wb
					↑R Amygdala - L MTG	ROI /wb
					↓R Amygdala - L/R Cerebellum	ROI /wb
					↓R Amygdala - R Superior parietal lobe	ROI /wb
					↓R Amygdala - L STG/MTG	ROI /wb
					↓R Amygdala - R Cuneus	ROI /wb
					↓R Amygdala - L MFG	ROI /wb
Singer et al., 2008	20	within	M	Empathetic responses to pain inflicted in self and others		
				Pain inflicted in self	↑R mOFC *(IFG)*	wb
					↑R lOFC *(MFG)*	wb

Author, year	Sample size	within/ between	Gender	Task *(contrast)*	Effect of oxytocin	wb/ ROI
					↓R Amygdala/Striatum *(GP)*	ROI
				Pain inflicted in self (prosocial>selfish)	↓L fronto-insular PFC *(MFG)*	wb
					↓L mPFC *(MFG)*	wb
				Pain inflicted in self (selfish>prosocial)	↓L Amygdala	wb
					↓R Amygdala *(parahippocampal gyrus)*	ROI
				Pain inflicted in other	↓R OFC *(IFG)*	wb
Sripada et al., 2012	15	within	M	*Resting state connectivity*	↑R Amygdala - ACC/rmFC	ROI /wb
Striepens et al., 2012	70	between	M	Implicit processing of social scenes using a memory task with negative and neutral pictures paired with nouns		
	35 placebo			*Later remembered negative > later forgotten neutral*	↑L anterior insula *(IFG)*	wb
	35 oxytocin			*Negative and neutral > baseline*	↑R Amygdala	ROI
				Negative > baseline	↑R Amygdala	ROI
				Neutral > baseline	↑R Amygdala	ROI
				Connectivity (all stimuli)	↓L Amygdala - L ACC	ROI /wb
				Connectivity (negative > neutral stimuli)	↓R Amygdala - L insula	ROI /wb
					↑L anterior insula - L IFG	ROI /wb
					↑L anterior insula - L basolateral Amygdala	ROI /wb
Wittfoth-Schardt et al., 2012	21	within	M	Implicit facial processing where fathers viewed pictures of their own child, a familiar and unfamiliar child		
				Implicit facial processing (own child > familiar child)	↓L Globus Pallidus	ROI
				Implicit facial processing (unfamiliar child > familiar child)	↓L Globus Pallidus *(Putamen)*	ROI
					↓L precentral gyrus	wb
					↓L Hippocampus *(Amygdala)*	ROI
					↓L/R MTG *(L STG/ R ITG)*	wb
					↓L STG	wb
					↓L supramarginal gyrus *(inferior parietal lobe)*	wb
				Implicit facial processing (own child > unfamiliar child)	↑L Caudate	wb

Author, year	Sample size	within/ between	Gender	Task *(contrast)*	Effect of oxytocin	wb/ ROI
				Connectivity (own child > familiar child)	↓L GP - R GP	ROI /wb
					↓L GP - L MFG	ROI /wb
					↓L GP - L Hippocampus	ROI /wb
					↓L GP - R superior parietal lobe	ROI /wb

ROI - Region of interest, wb - whole brain analysis; M = male; F= female; IU – International Units; ACC - Anterior Cingulate Cortex, MFG - Medial Frontal Gyrus, MTG - Medial Temporal Gyrus, STG - Superior Temporal Gyrus, ITG - Inferior Temporal Gyrus, SN - Substantia Nigra, PFC - Prefrontal Cortex, dlPFC - dorsolateral Prefrontal cortex, vlPFC - ventrolateral prefrontal cortex, mPFC - medial Prefrontal Cortex, rmPFC - rostral medial Prefrontal Cortex, IFG - Inferior Frontal Gyrus, OFC - Orbitofrontal Cortex, lOFC - lateral Orbitofrontal Cortex, mOFC - medial Orbitofrontal cortex, GP - Globus Pallidus

* also used patients with depression but only results for healthy controls are reported here **also used patients with social anxiety but only results for healthy controls are reported here

Areas in italics represent areas that were different when the coordinates were entered into Talairach client, all other areas are those reported by the studies listed

TABLE 5.3 – Overview of neural effects of oxytocin on different brain areas

Table 3a Effect of OXT on the Insula

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d
Baumgartner et al. (2010)	24	M	Trust interaction	trust game postfeedback	↓	0.92	↔	-
Domes et al. (2010)	24	F	Explicit facial processing	angry > neutral*	↑		↔	-
				fearful > neutral	↑		↔	-
				happy > neutral†	↑		↔	-
Riem et al. (2011)	24	F	listening to infant crying	infant cry > control noise*	↔	-	↑	
Rilling et al (2012)	24	M	Trust interaction	reciprocated cooperation	↔	-	↑	0.91
Striepens et al. (2012)	24	M	Implicit processing of social scenes	later remembered negative > later forgotten neutral†	↑	1.47	↔	-

Table 3b Effect of OXT on the Thalamus

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d
Baumgartner et al. (2008)	24	M	Trust interaction	trust game prefeedback	↔	-	↑	1.03
Domes et al. (2007)	24	M	Implicit facial processing	fearful > neutral	↓	1.69	↔	-
Domes et al. (2010)	24	F	Explicit facial processing	angry > neutral*	↑		↔	-
Labuschagne et al. (2012)	24	M	Explicit facial processing	sad > neutral	↑	1.27	↔	-

Table 3c Effect of OXT on the Basal Ganglia

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d	Area *(Talairach area)*
Baumgartner et al. (2008)	24	M	Trust interaction	trust game postfeedback	↓	0.81	↓	0.9	Caudate
					↔	-	↓	0.84	Caudate
					↔	-	↓	0.84	Caudate
					↓	0.92	↔	-	Putamen
Domes et al. (2010)	24	F	Explicit facial processing	fearful > neutral*	↔	-	↑		Brainstem *(SN)*
Lischke et al. (2012)	24	M	Emotion arousal rating task	negative > neutral scenes†	↔	-	↑		*Putamen (ROI)*
Pincus et al. (2010)	40	M/F	Explicit facial processing	across all facial valances	↑	1.97	↔	-	Caudate
				across all facial valances†	↑	2.12	↔	-	Caudate
					↑	1.86	↔	-	Globus Pallidus
Rilling et al. (2012)	24	M	Trust interaction	reciprocated cooperation	↑	1.03	↔	-	Caudate
					↔	-	↑	0.91	Putamen
Wittfoth-Schardt et al. (2012)	24	M	Viewing familiar or unfamiliar child	own child > unfamiliar child	↑		↔	-	Caudate
				own child > familiar child	↓		↔	-	Globus Pallidus
				unfamiliar child > familiar child†	↓		↔	-	Globus Pallidus *(Putamen)*

Table 3d Effect of OXT on the Temporal Lobes

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d	Area *(Talairach area)*
Domes et al. (2007)	24	M	Implicit facial processing	fearful > neutral	↓	1.44	↔	-	Inferior temporal lobe
					↓	1.38	↔	-	MTG
				happy > neutral	↓	1.45	↓	1.44	STG
					↓	1.38	↔	-	MTG
Domes et al. (2010)	24	F	Explicit facial processing	fearful > neutral	↑		↔	-	MTG (Temporal pole)
					↑		↔	-	STG

Table 3d Effect of OXT on the Temporal Lobes

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d	Area *(Talairach area)*
				happy > neutral	↑		↔	-	MTG (Temporal pole)
					↑		↔	-	STG
					↑		↔	-	fusiform gyrus
Labuschagne et al. (2012)	24	M	Explicit facial processing	happy > neutral	↔	-	↑	1.67	STG
Lischke et al. (2012)	24	F	Emotional arousal rating task	negative > neutral scenes	↑		↔	-	STG (temporal pole)
					↑		↔	-	MTG
					↑		↔	-	inferior temporal gyrus *(fusiform gyrus)*
Petrovic et al. (2008)	32	M	Fear conditioning to faces	main effect	↓	1.49	↔	-	MTG
				fear conditioning with direct gaze	↔	-	↓	1.49	Fusiform gyrus
Pincus et al. (2010)	40	M/F	Explicit facial processing		↑	1.97	↔	-	STG *(MTG)*
					↑	1.85	↔	-	STG *(MTG)*
Riem et al. (2011)	24	F	Listening to infant crying	infant cry > control noise	↑		↔	-	planum polare *(STG)*
Wittfoth-Schardt et al. (2012)	24	M	Viewing familiar or unfamiliar child (implicit facial processing)	unfamiliar child > familiar child	↓		↓		MTG
					↓		↔	-	STG

Table 3e Effect of OXT on the PFC

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d	Area *(Talairach area)*
Domes et al. (2007)	24	M	Implicit facial processing	fearful > neutral	↓	1.38	↔	-	MFG *(dlPFC)*
Domes et al. (2010)	24	F	Explicit facial processing	fearful > neutral	↔	-	↓		dlPFC
				angry > neutral	↑		↑		vlPFC
					↔	-	↑		dlPFC
				happy > neutral	↔	-	↓		dlPFC

Table 3e Effect of OXT on the PFC

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d	Area *(Talairach area)*
				happy > neutral	↓	1.39	↔	-	MFG
					↔	-	↓	1.29	mPFC
					↔	-	↓	1.21	mPFC
Petrovic et al. (2008)	32	M	Fear conditioning	main effect	↔	-	↓	1.66	vlPFC
				direct gaze	↓	1.9	↓	2.02	vlPFC
Pincus et al. (2010)	40	M/F	Explicit facial processing		↔	-	↑	1.87	Inferior frontal gyrus
Rilling et al. (2012)	24	M	Trust interaction	unreciprocated cooperation	↑	0.92	↔	-	vlPFC
					↑	0.92	↔	-	vmPFC
Singer et al. (2008)	32	M	Observing pain inflicted in self and others	pain in self	↔	-	↑		mOFC
					↔	-	↑		lOFC
				pain inflicted in self (prosocial > selfish)	↓		↔	-	fronto-insular PFC
					↓		↔	-	mPFC
				pain inflicted in other	↔	-	↓		OFC

Table 3f Effect of OXT on the Amygdala

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d	ROI/whole brain
Baumgartner et al. (2008)	24	M	Trust interaction	trust game postfeedback	↓	-	↓	-	wb
Domes et al. (2007)	24	M	Implicit facial processing	fearful > neutral	↓	-	↓	0.91	ROI
				angry > neutral	↓	-	↓	1.05	ROI
				happy > neutral	↓	-	↓	0.91	ROI
Domes et al. (2010)	24	F	Explicit facial processing	fearful > neutral	↑	0.79	↔	-	wb
				happy > neutral*	↑	-	↑	0.39	wb

Table 3f Effect of OXT on the Amygdala

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d	ROI/whole brain
					↓	-	↔	-	ROI
			Gaze at faces	gaze preference to eyes	↑	0.99	↔	-	ROI
Kirsch et al. (2005)	27	M	Implicit facial and scene processing	main effect for faces and scenes	↓	1.02	↔	-	ROI
				main effect for faces	↓	0.83	↔	-	ROI
				main effect for scenes	↓	0.74	↔	-	ROI
Labuschagne et al. (2010)	24	M	Implicit facial processing	angry > neutral	↓	-	↓	-	ROI
				fearful > neutral	↓	-	↓	-	ROI
				happy > neutral	↓	-	↓	-	ROI
Petrovic et al. (2008)	32	M	Fear conditioning (direct gaze)	gaze to negative stimulus > neutral	↔	-	↓	0.96	ROI
				main effect	↔	-	↓	-	ROI
Pincus et al. (2010)	40	M/F	Explicit facial processing	reading of the mind's eye task	↔	-	↑	1.33	wb
Riem et al. (2011)	24	F	Listening to crying babies	cry > control noise	↔	-	↓	0.43	ROI
Riem et al. (2012)	16	F	Listening to laughing babies	laughter > control noise	↓		↓		ROI
Rilling et al. (2012)	24	M	Trust interaction	reciprocated cooperation	↑	0.47	↔	-	wb
				[(reciprocated cooperation human > computer) OXT > (reciprocated cooperation human > computer) Placebo]	↑	1.03	↔	-	wb
Singer et al. (2008)	32	M	Empathy for pain	pain in self	↔	-	↓	0.64	ROI
				self, placebo > oxytocin, selfish > prosocial	↓	0.64	↔		wb
					↔		↓	0.75	ROI
Striepens et al. (2012)	24	M	Implicit scene processing and subsequent memory test	negative and neutral > baseline	↔	-	↑		ROI
				negative > baseline	↔	-	↑		ROI
				neutral > baseline	↔	-	↑		ROI

Table 3f Effect of OXT on the Amygdala

Author (year)	Dose	Gender	Task	Contrast	Left	Cohen's d	Right	Cohen's d	ROI/whole brain
Wittfoth-Schardt et al. (2012)	24	M	Viewing familiar or unfamiliar child	viewing own child, familiar child, unknown child	←→	-	←→	-	ROI

the arrows indicate the direction of differences in BOLD response during the selected contrast (significant differences are highlighted in bold: $p<0.05$); studies that did not provide enough information to calculate effect size were left blank; all doses are in IU, intranasal units; OXT = oxytocin; M = male; F= female; ROI = region of interest; wb = whole brain; MFG = Medial Frontal Gyrus; MTG = Medial Temporal Gyrus; STG = Superior Temporal Gyrus; SN = Substantia Nigra; PFC = Prefrontal Cortex; dlPFC = dorsolateral Prefrontal cortex; vlPFC = ventrolateral prefrontal cortex; mPFC = medial Prefrontal Cortex; IFG = Inferior Frontal Gyrus; OFC = Orbitofrontal Cortex; lOFC = lateral Orbitofrontal Cortex; mOFC = medial Orbitofrontal cortex; GP = Globus Pallidus

5.3.3 FMRI STUDIES IN HUMANS

5.3.3.1 REWARD SYSTEM

Social learning is largely influenced by how reward is processed in the reward system and can be modulated by oxytocin manipulation. The reward system is influential in social behaviour by driving the evaluation and interpretation of choices and their associated values (Adolphs, 2003). It also houses a large proportion of the oxytocin receptors in the human brain, the highest concentration of which is located in the substantia nigra (SN) (Loup et al., 1991; Loup et al., 1989), an area heavily implicated in reward processing and prediction error and dopamine signalling (Gimpl and Fahrenholz, 2001; Loup et al., 1991; Loup et al., 1989). However, this area is very small, and its between subjects variability makes it difficult to show robust activation in human imaging studies. Thus, its relative omission from the current human imaging studies in oxytocin is not surprising. However, the SN still plays a role in reward mediated social behaviours due to its influence over other areas of the basal ganglia, such as the caudate and putamen, the limbic system, and other areas of the brain that have shown consistent changes in brain activity after oxytocin administration. After correcting for location by standardising to Talaraich coordinates, one study that had originally reported finding activation after oxytocin administration in the brainstem showed that oxytocin elicited increased activation in the right SN while explicitly processing fearful faces over neutral faces (Domes et al., 2010).

We examined six studies addressing the reward system after oxytocin administration (Baumgartner et al., 2008; Domes et al., 2010; Lischke et al., 2012; Pincus et al., 2010; Rilling et al., 2012; Wittfoth-Schardt et al., 2012), and we review the available evidence in each of the above areas of interest (Basal Ganglia: comprised of Caudate, Putamen,

and Globus Pallidum(GP)). We found that oxytocin administration has an effect over reward related learning in that it seems to increase activation associated with reward related learning in the Caudate while decreasing learning effects. It has a similar influence on activation in the Putamen but is specific to learning during social interactions. How oxytocin affects neural activity during social tasks in the GP is less clear but it appears to play a role in attachment. We review the available evidence in each of the above areas of interest below.

5.3.3.1.1 BASAL GANGLIA

We identified six studies addressing oxytocin effects on the activation within the basal ganglia (five using whole brain analysis) (Baumgartner et al., 2008; Domes et al., 2010; Lischke et al., 2012; Pincus et al., 2010; Rilling et al., 2012; Wittfoth-Schardt et al., 2012), see Table 5.3. The basal ganglia are important areas for reward processing in the brain and are comprised of: (i) the globus pallidum (GP) (Pincus et al., 2010; Wittfoth-Schardt et al., 2012), (ii) the substantia nigra (SN) (Domes et al., 2010), (iii) putamen (Baumgartner et al., 2008; Lischke et al., 2012; Rilling et al., 2012), (iv) caudate (Baumgartner et al., 2008; Pincus et al., 2010; Rilling et al., 2012; Wittfoth-Schardt et al., 2012) and (v) ventral striatum. Some of these areas, such as the ventral striatum, show strong connections to the amygdala (Adolphs, 2003) and are important in reward based learning, by interpreting actions and their corresponding outcomes to make future decisions (Adolphs, 2003).

5.3.3.1.1.1 CAUDATE

The caudate plays a role in feedback processing when there exists a perception of contingency between the action and outcome, especially when the task incorporates an element of trust (Gromann et al., 2013; King-Casas et al., 2005; Montague et al.,

2006; O'Doherty, 2004; Tricomi et al., 2004), therefore the caudate is an important region to address when exploring the effects of oxytocin administration as it may help modulate how decisions are made based on preconceptions of trust. Four studies have addressed the role of the caudate after oxytocin administration (Baumgartner et al., 2008; Pincus et al., 2010; Rilling et al., 2012; Wittfoth-Schardt et al., 2012). The correlation between action and outcome in terms of action contingency appears to be activated exclusively within the left caudate and activation correlates with prediction error during instrumental conditioning (O'Doherty, 2004; Tricomi et al., 2004). On the other hand, bilateral activation of the caudate is observed in games involving trust where increased activity was related to an "intention to trust" (King-Casas et al., 2005; Montague et al., 2006). Furthermore, increased activation within the caudate has been shown to correlate with more benevolent partners (Delgado et al., 2005a; King-Casas et al., 2005) by reinforcing actions which could potentially lead to further rewards (Tricomi et al., 2004). In a task using a simple trust interaction involving money between two parties, Baumgartner et al. (2008) found that activation in the bilateral caudate was attenuated by oxytocin administration after receiving feedback about the trustworthiness of a supposed human partner they had just interacted with. In contrast, using a standard Prisoner's Dilemma paradigm to explore trust, Rilling et al. (2012) found that the left caudate was significantly activated after oxytocin administration in response to trustworthiness in the form of reciprocated cooperation in human opponents but there was no change in activation in the caudate after unreciprocated cooperation thus reinforcing its role in action contingency. It is important to note that the differences between these findings may be attributed to the fact that Baumgartner et al. (2008) did not distinguish between trust affirming and trust negating trials or reciprocated and unreciprocated trust and, as such, the

difference in caudate activity may be due to differences in trial types between the studies. Another explanation for the diminished activity may be that caudate activation diminished as learning progressed or that they believed their partner to be morally "good" (Delgado et al., 2005a; Delgado et al., 2005b; King-Casas et al., 2005). Furthermore, the increased activation in the caudate after oxytocin administration may have predicted their belief in the likelihood of future cooperation (King-Casas et al., 2005).

The caudate is also of interest in other studies incorporating the processing of social stimuli such as novel and familiar faces. A study by Wittfoth-Schardt et al. (2012) had fathers view pictures of their own child, a familiar child and an unfamiliar child after being administered oxytocin. They reported that oxytocin administration increased activation in the left caudate when men viewed their own child versus an unfamiliar child. This may reflect the enhanced rewarding effects of parental attachment with one's own child - which is augmented by oxytocin administration. A study by Pincus et al. (2010) also showed an increase the neural activation in the left caudate after being administered oxytocin while assessing social stimuli during a reading of the mind's eyes task. Furthermore, Labuschagne et al. (2010) showed a main effect of oxytocin in the activation within the left caudate while explicitly processing emotional faces by matching angry, happy and fearful faces. These interactions may potentially reflect the neural effects of learning, attachment and evaluating novelty in terms of learning reward contingencies when combined with oxytocin administration, showing that oxytocin administration increases reward related responses while decreasing learning related activation.

5.3.3.1.1.2 PUTAMEN

The putamen is adjacent to the caudate and plays a role in associative learning (Haruno and Kawato, 2006). It has been demonstrated to show greater activation, relative to the caudate, during performance of actions associated with reward but shows similar levels of activation, relative to the caudate, when still learning the optimal action associated with a reward (Hikosaka et al., 2002). Three studies have addressed the changes in the activation of the putamen after being administered oxytocin (Baumgartner et al., 2008; Lischke et al., 2012; Rilling et al., 2012). Two studies included in the systematic review used trust interactions to demonstrate greater activation in the putamen extending into the insula after being given oxytocin and having received feedback about their partner (Baumgartner et al., 2008; Rilling et al., 2012). One study by Rilling et al. (2012) used a Prisoner's dilemma game to demonstrate greater activation in the right putamen as a response to reciprocated cooperation after oxytocin was administered. Another study used a trust game (King-Casas et al., 2005) to demonstrate an attenuation in the activation within the left putamen following feedback on a partner's trustworthiness after oxytocin administration (Baumgartner et al., 2008). A study in females by Lischke et al. (2012) showed that the right putamen was more active after receiving oxytocin when rating negative scenes over neutral scenes. However, the activation observed in the putamen was part of a region of interest analysis centred around the amygdala and activation in these regions was not evident during whole brain analysis. Overall, the putamen only showed reliable changes in activation after oxytocin administration during games involving trust manipulations and when there was concurrent activation within the caudate. Therefore, the putamen may play a role, alongside the caudate, during the processing of rewards related to interactions with other people.

5.3.3.1.1.3 GLOBUS PALLIDUS (GP)

Another area of the reward system that has been implicated in oxytocin studies, albeit to a lesser extent, is the GP, which has been associated with general reward signal processing (Hong and Hikosaka, 2008) as well as maternal attachment (Bartels and Zeki, 2004; Leibenluft et al., 2004). Although we recognise that the GPe and GPi have different functions, restrictions in the number of studies involving the GP made it difficult to draw further conclusions on subsections. Two studies have addressed oxytocin administration on activation within the GP (Pincus et al., 2010; Wittfoth-Schardt et al., 2012). A recent study by Wittfoth-Schardt et al. (2012) showed that oxytocin administration attenuated activity in the GP when viewing one's own child versus viewing a familiar child as well as viewing an unfamiliar child versus a familiar child. This suggests a role for oxytocin administration in attenuating activation in the GP related to reward and novelty and also coincides with areas associated with maternal attachment (Bartels and Zeki, 2004; Leibenluft et al., 2004).. The earlier study by Pincus et al. (2010) also showed an effect of oxytocin administration in the activation within the left GP during a reading of the mind's eye task. However, these findings in the GP after oxytocin administration have not been robustly replicated.

5.3.3.2 TEMPORAL LOBES

Although primarily known for their role in auditory processing (Simons et al., 2010) and vision, the temporal lobes also play an important role in memory and the interpretation of social cues through visual processing and spatial recognition to help determine socially relevant information (Adolphs, 2001; Allison et al., 2000). The temporal lobes are also known to be a target of output from the basal ganglia (Middleton and Strick, 1996) which may show how oxytocin administration influences

neural processes in this area through learning and reward processing of social stimuli. Of the areas in the temporal lobe, the middle and superior temporal gyrus (MTG and STG) have been shown to be consistently activated in studies involving human emotional face processing (Fusar-Poli et al., 2009) and during mentalising, or theory of mind (Fett et al., 2013; Frith and Frith, 2005; Hampton et al., 2008). Eight of the twelve studies reporting whole brain findings found differential activation in the temporal lobe after oxytocin administration, most of which used faces as social stimuli (Domes et al., 2007a; Domes et al., 2010; Labuschagne et al., 2011; Lischke et al., 2012; Petrovic et al., 2008; Pincus et al., 2010; Riem et al., 2011; Wittfoth-Schardt et al., 2012), see Table 5.3. Additionally, another study found that connectivity to the temporal lobe from the amygdala was increased after oxytocin administration (Rilling et al., 2012). This consistency of activation made this the most robust region showing activation after oxytocin administration.

Domes et al. (2007a) used implicit facial processing in men to demonstrate decreases in the activation within the left MTG and bilateral STG after oxytocin administration in response to happy facial stimuli; as well as increased activation within the left inferior temporal lobe and MTG in response to fearful facial stimuli. On the other hand, Domes et al. (2010) used an explicit facial processing task in women to show increased activation in the left MTG and STG after oxytocin administration in response to happy and fearful facial stimuli. Labuschagne et al. (2010) used explicit and implicit processing tasks in males to show a main effect of oxytocin administration on the activation within the left MTG and bilateral STG when implicitly processing a range of emotional faces, although the direction of this effect was not reported. In a follow-up report, Labuschagne et al. (2011) showed increased activation within the right STG

after oxytocin administration while explicitly processing happy faces. Wittfoth-Schardt et al. (2012) also showed that, in men, activation is attenuated in the bilateral MTG and left STG after oxytocin administration when implicitly processing the faces of an unfamiliar child versus a familiar child. This effect of oxytocin administration on neural attenuation associated with facial valence is not just limited to the processing of faces but extends to influencing activity where negative stimuli have been paired with faces. In a task pairing a shock with different faces to condition for fear, Petrovic et al. (2008) showed attenuation in the activation within the right anterior MTG after being administered oxytocin across all fear conditioning trials. However, increased activity when viewing faces appears to be mainly evident in women as Lischke et al. (2012) asked women to rate the emotional arousal from a series of faces, and demonstrated greater activation in the STG and inferior temporal gyrus (ITG) after being administered oxytocin. Furthermore, a study by Pincus et al. (2010) using mainly women (8 out of 9 subjects) showed greater activation in the STG after being administered oxytocin during the reading of the mind's eye task. A similar increase in activation within the STG activation was reported in women administered oxytocin before auditory stimuli of crying infants by Riem et al. (2011). It is important to note that all of these studies in women used explicit emotional processing - except for the study by Riem et al. (2011) - while the studies in the men used tasks with implicit facial processing - except the study by Labuschagne et al. (2011) who also showed increased activation in the temporal lobes after oxytocin administration, contrary to other studies in males. Thus, task type, as well as gender, may play a large role in how oxytocin administration affects neural activity in the temporal lobes.

Of the areas in the temporal lobes associated with social processing, the fusiform gyrus has been the area most consistently activated in response to tasks incorporating facial stimuli (McCarthy et al., 1997a) and is known to be modulated by facial valence (Pujol et al., 2009). Neural activity in this area has also been shown to be modulated by oxytocin administration. In women, Domes et al (2010) (Domes et al., 2010) showed an increase in activation across various regions of the temporal lobes after being administered oxytocin when viewing fearful and happy faces but not angry faces. However, in men, Petrovic et al. (2008) showed a decrease in activation in the left MTG and right fusiform gyrus following oxytocin administration after fear conditioning using faces with direct gaze. Overall, oxytocin administration appears to play a role in the increase and decrease of activity in the temporal lobes with gender specific effects; where oxytocin administration increases activation in the temporal lobes in women and generally attenuates activation in the temporal lobes in males. However, this difference in activation by gender within the temporal lobes may also be due to the variability in task types; oxytocin administration may attenuate activation in the temporal lobes during implicit facial processing but may increase activation in the temporal lobes during explicit facial processing.

5.3.3.3 INSULA

The activation of the insula after oxytocin administration may reflect neural processing to minimise risk prediction errors (Preuschoff et al., 2008) and reward anticipation in a social context (Villafuerte et al., 2012; Wittmann et al., 2010). Activity in the insula may also be associated with emotion regulation(Phan et al., 2002b) and facilitating a sense of emotional involvement when interacting with others in a trust game (Singer et al., 2004). Its activation during trust games implicates it in making decisions about the risk

of trusting another person during social interactions. Five studies in our review have investigated neural activity in this area (Baumgartner et al., 2008; Domes et al., 2010; Riem et al., 2011; Rilling et al., 2012; Striepens et al., 2012). Overall, activity in the insula is generally augmented after oxytocin administration, suggesting a heightened role in modulating risk prediction and reward anticipation in a social context. There does not appear to be a significant effect by gender in this area. Furthermore, our meta-analysis of all whole brain imaging data found the left insula to be the most robustly activated area between all the studies included in the meta-analysis (Figure 5.2).

In a trust game, Baumgartner et al. (2008) showed attenuation of activation within the left putamen and insula after oxytocin administration in response to all feedback about their partner's trustworthiness while Rilling et al. (2012) demonstrated an increased activation in the right putamen and insula after oxytocin administration following reciprocated cooperation but not unreciprocated cooperation. This may show a lateralisation of oxytocin's effect on the processing of trust related stimuli in the putamen and insula or may reflect a difference caused by cooperation bias that was not explicitly established by Baumgartner et al. (2008) as they did not differentiate between cooperative and uncooperative trials.

The insula is also important in evaluating tasks with an element of emotional processing. Domes et al. (2010) found that, in women only, oxytocin administration intensified activation in the insula in response to fearful and happy emotional faces compared to neutral faces when asked to identify gender. Another study in women by Riem et al. (2011) also demonstrated a greater activation within the insula after being administered oxytocin and listening to a crying infant. This effect may reflect an

implicit empathising that is intensified by oxytocin administration in women but not men. However, using men, Striepens et al. (2012) also showed an increase in activation within the left anterior insula after being given oxytocin when viewing negative social scenes that were later remembered over neutral social scenes that were later forgotten. This may reflect the role of the insula in the recall of emotional information. They went on to show that the connections between the insula and other regions were also important in determining which negative social scenes were remembered over neutral social scenes after being administered oxytocin. Furthermore, functional connectivity increased between the left anterior insula and the left inferior frontal gyrus (IFG) as well as the left basolateral amygdala after being administered oxytocin. However, connectivity between the right amygdala and left insula was attenuated after receiving oxytocin. Of these areas, the basolateral amygdala was shown to be the major projection area of oxytocin-related sharing of information between the left insula and the left amygdala, suggesting that the insula may have been using some of the modulatory functions of the amygdala to bias emotional processing (Striepens et al., 2012).

5.3.3.4 LIMBIC AND PARALIMBIC SYSTEM

The limbic system is important in the regulation of autonomic and endocrine functioning as well as the processing and response to emotional stimuli (for a review see (Phan et al., 2002b)).

All of the fMRI studies presented in this review have investigated some aspect of the limbic system (Baumgartner et al., 2008; Domes et al., 2007a; Domes et al., 2010; Gamer et al., 2010a; Kirsch et al., 2005; Labuschagne et al., 2010, 2011; Lischke et al., 2012; Petrovic et al., 2008; Pincus et al., 2010; Riem et al., 2011; Rilling et al., 2012;

Singer et al., 2008; Sripada et al., 2012; Striepens et al., 2012; Wittfoth-Schardt et al., 2012). Its role has been one of the focuses of neuroendocrine research, most notably oxytocin, and has mainly revolved around the role of the amygdala, which is explored in greater detail below. This systematic review explores the role of other areas in the limbic system in addition to the amygdala and their contribution and importance for this neuropeptide.

5.3.3.4.1 AMYGDALA

In all the fMRI studies involving oxytocin administration retrieved in the present systematic review, aside from one (Wittfoth-Schardt et al., 2012), one of the main regions of interest was the amygdala, see Table 5.3. Its involvement in numerous animal studies have implicated it as an important area for oxytocin binding and release (Gimpl and Fahrenholz, 2001; Huber et al., 2005). In humans, its role in social cognition (Adolphs et al., 1998) and, notably, facial processing (Fusar-Poli et al., 2009) have established the amygdala as a very important region in oxytocin research. Although no oxytocin receptors have been detected in the amygdala in any human studies (Gimpl and Fahrenholz, 2001; Loup et al., 1991; Loup et al., 1989) its size in humans has been shown to vary in relation to the oxytocin gene (Furman et al., 2011; Inoue et al., 2010) and it is consistently implicated in studies involving oxytocin administration (Table 5.3).

Studies using implicit processing of social stimuli consistently found attenuated activation within the amygdala after being administered oxytocin (Domes et al., 2007a; Kirsch et al., 2005; Petrovic et al., 2008; Riem et al., 2011). However, pairing implicit facial processing with a negative stimulus to condition for fear showed non-significant attenuation in the amygdala (Petrovic et al., 2008). In tasks using explicit processing of social stimuli, there were more mixed results for the direction of activation in the

amygdala resulting from oxytocin administration. However, when separating for gender, in studies involving all or mainly females, oxytocin administration increased activation in the amygdala (Domes et al., 2010; Pincus et al., 2010) but in males oxytocin administration attenuated activation in the amygdala (Gamer et al., 2010a). In a study involving a trust interaction, oxytocin administration increased activation in the amygdala when cooperation was reciprocated and this increase in activation was shown to be specific to when a subject was told they were playing another human versus a computer. These studies show that the type of study and gender play a large role in how oxytocin influences activity in the amygdala. It is also important to note that only three of these studies reported activation in the amygdala significant at a whole brain level (Domes et al., 2010; Rilling et al., 2012; Singer et al., 2008); the majority of these studies used region of interest (ROI) analysis or small volume correction (SVC) to extract significant activation within the amygdala. Two other studies used ROI analysis and reported insignificant findings bilaterally (Baumgartner et al., 2008; Labuschagne et al., 2010). Furthermore, our meta-analysis of all studies reporting whole brain fMRI findings did not show any hypo- or hyperactivation of the amygdala in response to oxytocin administration during tasks using emotional stimuli (Figure 5.2, Table 5.4).

5.3.3.5 THALAMUS

The thalamus has been implicated in various studies involving oxytocin administration. Its involvement may be due to its connections with other regions of the brain which help mediate and control social interactions and behaviour. In addition to serving as the brain's relay board, the thalamus has been associated with selective attention and levels of arousal (Baumgartner et al., 2008; Portas et al., 1998) as well as consciousness

(Posner, 1994) and may be utilised to relay and modulate important emotional and cognitive information (Shane et al., 2008). During a trust game, oxytocin administration increased the amount of activity in the right thalamus before being given feedback on the outcome of the game (Baumgartner et al., 2008). However, in an implicit emotion processing task where subjects viewed faces of varying facial valence at varying intensities, oxytocin administration attenuated activation in the left thalamus in response to angry faces (Domes et al., 2007a) and in another study using explicit emotional processing, where subjects had to match faces with the same facial valence, there was a main effect of oxytocin administration in the left thalamus for sad facial valence (Labuschagne et al., 2010) and angry facial valence (Domes et al., 2010). Together, these findings may reflect differential mediation and relaying of signals from emotional stimuli to corresponding areas connected to the thalamus which varies with task design.

5.3.3.6 PREFRONTAL AND ANTERIOR CINGULATE CORTEX

One area associated with the limbic system is the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC). Most of the imaging studies using males have shown that oxytocin administration attenuates activation within both of these regions during the processing of social stimuli (Baumgartner et al., 2008; Labuschagne et al., 2011; Petrovic et al., 2008; Singer et al., 2008). Overall, the studies show that, at least in men, the involvement of the OFC and ACC are minimised after oxytocin administration. Furthermore, attenuated activity in the dorso and ventrolateral PFC after oxytocin administration may be indicative of an attenuated need for emotion regulation and cognitive control.

The PFC is important for social interactions due to its role in aiding action selection and evaluation (Kennerley et al., 2011) as well as facial processing (Fusar-Poli et al., 2009) and mentalising, or interpreting the actions of others (Frith and Frith, 2005). Specifically, the roles of the ACC and orbitofrontal cortex (OFC) are important in helping to compute the value of various choices (Kennerley et al., 2011). More specifically, the OFC is important for evaluating current choices while the ACC encodes choice predictions (Kennerley et al., 2011). Most of the imaging studies using males have shown that oxytocin administration attenuates both of these regions during the processing of social stimuli(Baumgartner et al., 2008; Labuschagne et al., 2011; Petrovic et al., 2008; Singer et al., 2008). However, one study in mainly females, showed an increase in activation within the ACC after being administered oxytocin and performing a reading of the minds eyes task (Pincus et al., 2010). This may reflect a gender difference in how social stimuli are evaluated after being administered oxytocin but there are not enough studies to reach a strong conclusion. Overall, the studies show that, at least in men, the involvement of the OFC and ACC are minimised after oxytocin administration and may indicate a greater efficiency in evaluating social stimuli.

Other areas of the prefrontal cortex (PFC) such as the dorsolateral PFC (dlPFC), which is involved in cognitive control (Rilling and Sanfey, 2011; Wood and Grafman, 2003), and ventrolateral PFC (vlPFC), which is implicated in emotion regulation (Ochsner and Gross, 2005), also play a role in encoding and processing value and activation within these regions are also shown to be attenuated by oxytocin administration in response to explicit and implicit facial processing (Domes et al., 2007a; Domes et al., 2010; Petrovic et al., 2008; Rilling et al., 2012). This effect is stable across genders and

different task types except in part of one study where females explicitly processing an angry face over the neutral face showed increased activation in the bilateral vlPFC and right dlPFC after oxytocin administration (Domes et al., 2010). However, in this same study, they also found that activation in the dlPFC was attenuated for fearful and happy faces after oxytocin administration. There is evidence that females process angry faces differently than men in the PFC (Fusar-Poli et al., 2009; McClure et al., 2004). Females show greater activation in the PFC while explicitly processing angry faces as opposed to neutral faces with no difference in happy or sad faces (McClure et al., 2004) which may be why females exhibit this difference in activation with regard to facial valance after oxytocin administration. Thus attenuated activation in these areas after oxytocin administration may be indicative of an attenuated need for emotion regulation and cognitive control.

5.3.4 EEG STUDIES IN HUMANS

Studies using EEG have demonstrated how oxytocin administration can attenuate cortical activity and its relationship to social tasks (Fehm-Wolfsdorf et al., 1988; Huffmeijer et al., 2012a; Perry et al., 2010). To date, only five studies have used EEG and oxytocin in humans and only two have explored the social implications of altered cortical activity due to oxytocin administration while performing a task with social stimuli (Born, 1987; Fehm-Wolfsdorf et al., 1988; Huffmeijer et al., 2012a; Huffmeijer et al., 2012b; Perry et al., 2010) (Table 5.1).

A few studies have been done using EEG and oxytocin administration without incorporating any social elements. Unsurprisingly, these studies did not find any effect of oxytocin administration. A study by Fehm-Wolfsdorf et al. (1988) explored the potential for oxytocin administration to facilitate non-social learning and long-term

recall of 25 unrelated nouns and the effect on auditory evoked potentials using a series of tone pips. Another study by Born (1987) administered oxytocin in a task while subjects performed an auditory mismatch task, no difference was found in cortical activity after oxytocin administration. Both of these experiments highlight that oxytocin administration did not appear to have any systematic effect on brain activity in tasks lacking social elements.

To demonstrate that oxytocin administration can have an effect over cortical activity during social tasks, Perry et al. (2010) used EEG and oxytocin along with stimuli that demonstrated biological motion. Subjects were presented with a series of point-lights that reflected either biological or non-biological movements. After being administered oxytocin, subjects demonstrated improved performance between trials associated with biological movement versus those with random movement, and also elicited wide-spread mu and alpha suppression compared to being administered a placebo. This change in mu/alpha activity may be indicative of potential processing of higher social information as well as activation of the mirror neuron system (Oberman et al., 2007). Another study with social stimuli explored the cognitive effects of charitable donations and their modulations by oxytocin administration. Huffmeijer et al. (2012a) measured frontal alpha asymmetry and parental love withdrawal, a measure of how often their parents would withhold love and affection to discipline their children for misbehaving or failing to attend to an instruction, after oxytocin and placebo administration and then gave participants a chance to donate to a charitable organisation. They found that in subjects with lower love withdrawal and relative lower right to left frontal alpha activity, oxytocin administration increased charitable donations. Additionally, subjects that showed higher relative left frontal activity gave

larger donations than those with higher relative right frontal activity. No differences in frontal alpha asymmetry were found after oxytocin administration; however, EEGs were only recorded at rest, with no social or cognitive probes which may be why no changes were observed. Huffmeijer et al. (2012b) went on to use faces as a social probe in women. They used the Eriksen flanker task (Eriksen, 1974) in which each trial was followed by either a happy or disgusted face and an indicator as to whether or not they were correct. They found that oxytocin administration increased the amplitudes of the vertex positive potential (VPP) and late positive potential (LPP) which indicated greater attention to the feedback stimuli (from the LPP) and an increased ability to process faces (from the VPP) regardless of the facial valence or feedback. This finding supports fMRI data showing that oxytocin administration has an effect over facial valence perception as well as showing that perception of facial valence is altered across both early (VPP) and later (LPP) stages of processing. Overall, these studies show how using EEG can increase our understanding of how oxytocin administration exerts its influence over cortical activity in addition to haemodynamic findings and how these changes in neural activity may influence social cognition.

These studies show altered EEG activity after oxytocin administration corresponding with changes in performance on social tasks. No effects were found in experiments without a social aspect, highlighting that oxytocin does not appear to have any systematic effect on brain activity in tasks lacking social elements. The study by Perry et al. (2010) is particularly important as it highlights the specificity of cortical activity elicited by oxytocin administration in a social context. This study also highlights the importance of oxytocin administration in manipulating widespread cortical activity and provides a possible translation to the importance of mirror neurons and their

association with oxytocin administration. Collectively, these studies show how using EEG can increase our understanding of how oxytocin administration exerts its influence over cortical activity in addition to haemodynamic findings and give a more complete picture of how oxytocin administration may influence social cognition.

5.3.5 EFFECT SIZES

The magnitude of the effect of oxytocin administration described above here is provided for each ROI in the Table 5.3. For the human fMRI studies, we observed a Cohen's d ranging from 0.39 to 2.12 for the emotional tasks, 0.47 to 1.03 for the social cognition tasks involving trust.

The largest effect size was observed in the temporal lobes (1.56 ± 0.21). This reflects the large number of studies that showed activity in the temporal lobes, mainly during tasks incorporating facial processing.

The smallest effect size was observed in the amygdala (0.82 ± 0.24). This smaller effect may be due to the large number of studies that used a region of interest approach to show that the amygdala was significant in their study.

5.3.6 VOXEL BASED META-ANALYSIS

We performed a meta-analysis using all studies which reported whole-brain findings using emotional stimuli. A total of 11 studies fit all the criteria and were included in the meta-analysis (Domes et al., 2007a; Domes et al., 2010; Gimpl and Fahrenholz, 2001; Labuschagne et al., 2011; Lischke et al., 2012; Petrovic et al., 2008; Pincus et al., 2010; Riem et al., 2011; Singer et al., 2008; Striepens et al., 2012; Wittfoth-Schardt et al., 2012). Taking into account one and two sample studies, we found that the left insula was the only area that reliably showed greater activation after oxytocin administration

across all studies (Figure 5.2 and Table 5.4). These findings were found across all task types and genders, and thus may have important implications for the role of oxytocin research by showing that oxytocin administration augments neural responses to social tasks in the left insula independent of task type and gender.

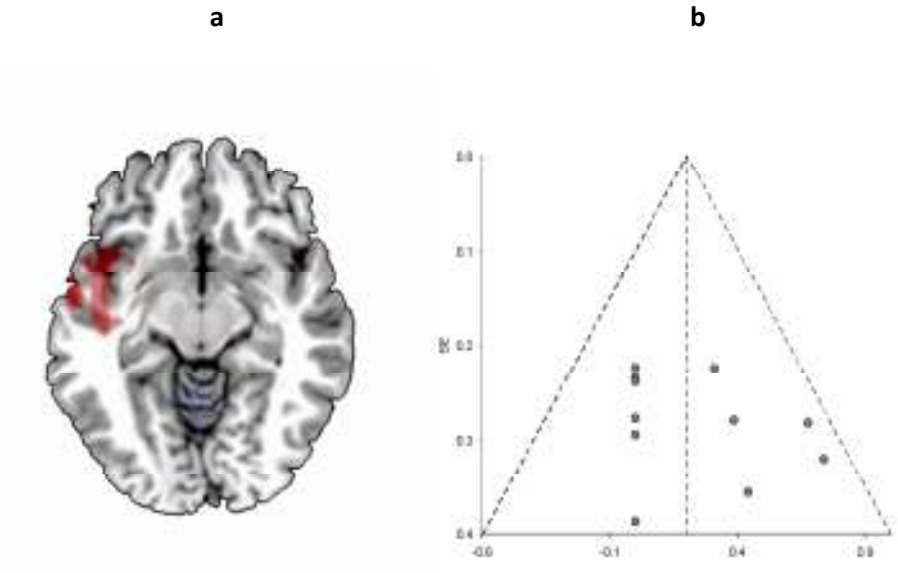

FIGURE 5.2 - Results for voxel based SDM meta-analysis of placebo controlled fMRI studies employing acute oxytocin challenge in humans

TABLE 5.4 - Results for voxel based SDM meta-analysis of placebo controlled fMRI studies employing acute oxytocin challenge in humans

	Peak			Cluster	
	Talairach	**Z**	**P**	**Voxels**	**Breakdown**
Oxytocin > Placebo					
Left insula (extending to superior temporal gyrus and precentral frontal gyrus)	-46,-6,-6	2.451	0.0000003	1182	Left BA 13 (222) Left BA 22 (219) Left BA 38 (174) Left BA 6 (165) Left BA 21 (120) Left BA 43 (70) Left BA 44 (39) Left BA 4 (37) Left BA 47 (31) Left BA 42 (26) Left BA 9 (19) Left BA 20 (12)
Oxytocin < Placebo					
(none)					

Results were thresholded with voxel p ≤ 0.005 uncorrected, peak z ≥ 2, and cluster extent ≥ 10 voxels.
Breakdown regions with an extent < 10 voxels extent are not reported.

5.4 DISCUSSION

In the present study, we have addressed the acute effect of oxytocin administration on neural activity within the brain. Firstly, we have conducted a systematic review of the neurophysiological and electrophysiological placebo-controlled studies administering oxytocin. Secondly, we have measured the magnitude of change in activation of various brain regions as a result of oxytocin administration versus a placebo in specific key areas relevant to the behavioural effects of oxytocin. Lastly, we have provided the first fMRI voxel-based meta-analysis of the effects of oxytocin administration. We found that gender and task type seem to significantly impact the neurophysiological effects of oxytocin administration. The biggest effect sizes from oxytocin administration were observed in the temporal lobes and the smallest were observed in the amygdala. The fMRI voxel-based meta-analysis revealed significant insular hyperactivation during the oxytocin administration vs placebo contrasts.

Our systematic review indicates that oxytocin administration appears to influence different brain regions in varying ways. In the reward system, oxytocin administration acts to increase activity related to social reward while decreasing learning social contingencies, this is the most evident during the evaluation of tasks involving trust and reciprocity (Baumgartner et al., 2008; Rilling et al., 2012). In the temporal lobes, the modulation of neural activity after oxytocin administration varies according to task type and gender. fMRI studies in women have shown that oxytocin exerts an almost opposite effect to that seen in men. However, most of the tasks in women used explicit emotional processing while most of those in men used implicit emotional processing (for a meta- analysis of brain activation during explicit vs implicit emotional processing see (Fusar-Poli et al., 2009)). Explicit emotional processing tasks in females

tended to augment activity in the temporal lobes after oxytocin administration (Domes et al., 2010; Lischke et al., 2012; Pincus et al., 2010) while implicit emotional processing in males tended to attenuate activity after oxytocin administration (Domes et al., 2007a; Petrovic et al., 2008; Wittfoth-Schardt et al., 2012).

This may show that the manner in which each gender attends to social information varies but it may also reflect the differences in how oxytocin administration modulates activity based on task type. This shows the importance of the temporal lobes in processing social stimuli and shows how oxytocin administration influences how social stimuli are perceived and how socially salient information is attended to.

There is a consistent association with oxytocin administration and amygdala function in human oxytocin studies with widespread region of interest and small volume correction around the amygdala. Our systematic review supports this view by showing consistent attenuation of amygdala activity in implicit emotion judgement in men. However, the negative results in our voxel-wise meta-analysis uncovers relevant heterogeneity among the surveyed studies, most notably between men and women, and between implicit and explicit tasks. It is still unclear whether or not the amygdala has any oxytocin receptors. So far, only one group has unsuccessfully attempted to localise oxytocin receptors in the amygdala, using a relatively nonspecific approach (autoradiography) (Loup et al., 1991; Loup et al., 1989). More studies are necessary to clearly show or exclude oxytocin receptor presence and abundance in human brain. However, magnocellular oxytocin neurons project to areas such as the central amygdala (Sofroniew et al., 1981) which may indicate one way in which oxytocin influences the amygdala. Recent PET imaging in rats has identified a potential ligand to look at oxytocin receptor density (Smith et al., 2013a) which may give better insight

into the receptor densities in humans in the future, although recent research by the same group has also shown this particular radiotracer may have limited brain penetration in primates (Smith et al., 2013b).

There is evidence linking midbrain and mesolimbic dopamine with the effects of oxytocin on the processing of social stimuli**.** Some evidence suggests that dopamine is involved in mediating some of the same maternal behaviours that are exhibited under the influence of oxytocin (Douglas, 2010; Shahrokh et al., 2010) as well as pair bonding (Smeltzer et al., 2005, 2006b; Strathearn, 2011; Wang and Aragona, 2004). Furthermore, oxytocin has been implicated in helping to mediate addiction and withdrawal in the mesolimbic dopaminergic pathways (Baskerville and Douglas, 2010b) and differences in peripheral and central levels of oxytocin have been found in patients with disorders with potential dopamine abnormalities such as autism (Al-Ayadhi, 2005; Anderson et al., 2008; Hamilton et al., 2013; Previc, 2007), schizophrenia (Howes et al., 2012; Howes and Kapur, 2009; Laruelle and Abi-Dargham, 1999; Sasayama et al., 2012a; Winton-Brown et al., 2014) and social anxiety disorder (Bell et al., 2013; Fink et al., 2009; Hoge et al., 2008; Schneier et al., 2009). Additionally, preclinical studies have shown that dopaminergic fibres may regulate oxytocin release (Lindvall et al., 1984; Melis and Argiolas, 2011) and that the receptor binding sites and neuronal fibres of both of these neurochemicals reside in the same regions of the CNS and are often next to each other (Baskerville and Douglas, 2010b; Schwartz et al., 1994; Smeltzer et al., 2006a). Further evidence suggests that, at least in the ventral and dorsal striatum, D_2 dopamine receptors and oxytocin are heteromers with facilitatory receptor to receptor interactions (Romero-Fernandez et al., 2012). Although most studies providing links between dopamine and oxytocin have been done in a preclinical population and most

evidence for a relation between dopamine and oxytocin in humans is speculative, a few recent studies in humans have also shown these two systems to be more directly related. Sauer et al. (2013) found a relationship between oxytocin genes, dopamine and oxytocin administration during responses to social stimuli. They postulated that the availability of dopamine may regulate oxytocin secretion within the amygdala. Furthermore, Love et al. (2012) found that dopaminergic responses to stress could be explained by variability within the oxytocin gene. Evidence from these studies above lead to the proposal that dopamine and oxytocin may work together to regulate behavioural responses to social stimuli, such that dopamine affects the assignment of emotional salience (Fett et al., 2012; Winton-Brown et al., 2014) while oxytocin modulates amygdala tone (Rosenfeld et al., 2011). However, further review of the relationship between dopamine and oxytocin is outside the scope of this paper and we would encourage those interested to look at reviews already available on this subject (Abi-Dargham, 2012; Baskerville and Douglas, 2010a; Love, 2014; Rosenfeld et al., 2011; Skuse and Gallagher, 2009).

Finally, our fMRI voxel-based meta-analysis clearly showed the insula is consistently modulated by oxytocin administration across all task types and genders. The insula is known for its role in emotion regulation by aiding in the recall and self-induction of emotion (Phan et al., 2002b) as well as facilitating a sense of empathy under uncertainty (Singer et al., 2009). In the context of processing emotional stimuli after oxytocin administration, the role of the insula may be one of increased recall of emotional information by self-induction of these emotions. Connectivity analyses have shown that, after oxytocin administration, connectivity between the insula and other areas important to social cognition, such as the amygdala, increases (Rilling et al.,

2012; Striepens et al., 2012). Despite this intriguing result, there are many potential confounding factors which were hard to account for and may have biased the voxel-based analysis. It is important to note that this meta-analysis was only done with relatively few studies (n = 11) therefore it was difficult to conduct moderator analysis to take into account different study design characteristics that may have affected effect sizes. Thus our work represents a more preliminary analysis of the general effects of oxytocin administration without taking into account factors such as gender, past experiences, and in-group versus out-group. For example, in some areas of the brain, such as the temporal lobes, there is a strong indication that females and males have opposite patterns of activity as a result of oxytocin administration. This may have caused some areas to appear as null which in a gender specific analysis may have been significant. However, we did not have enough studies in each gender to test this hypothesis. Additionally, the type of task varied between studies but no specific type of task had enough power to create its own meta-analysis, so results may have been biased in this regard too. As discussed above, it appears that implicit processing of social stimuli decreases activity while processing explicit stimuli increases activity, for example, in the amygdala. The significant activation of the insula in our meta-analysis highlights it as an important area to potentially include in further studies for further exploration.

5.5 CONCLUSIONS

Oxytocin is a complex molecule with many facets which have yet to be understood. Although it is clear that oxytocin administration has an effect on neural activity of cortical and subcortical areas over a range of social tasks, it is not clear yet precisely how oxytocin administration influences neural activity across these domains. We have

shown evidence that oxytocin may play differential roles across genders. The neurophysiological effects of oxytocin on subcortical areas such as the amygdala could also be influenced by task type. Indeed, our systematic review indicates small effect sizes in the amygdala, while our voxel-based meta-analysis indicates no effect in this region. Conversely, we found a significant effect of oxytocin administration in the left insula, which survived across all task types and genders. The temporal lobes were also shown to be influenced by oxytocin administration by our systematic review as these demonstrate the largest effect sizes across genders and task type.

5.6 FUTURE PERSPECTIVES

Further research into oxytocin and the areas it modulates are necessary to elucidate more on this neuropeptide. More studies looking at social tasks using oxytocin administration which incorporate differing neural domains will help clarify why oxytocin administration appears to attenuate activity in some tasks and genders and augment it in others. Looking at tasks which also implicate the reward system may also help elucidate the role of dopamine and its ties to oxytocin. oxytocin's current links to dopamine and its pronounced effects over tasks in the social domain mean that oxytocin is of particular interest to clinical groups (Ferris, 2008). Preliminary studies have shown its potential efficacy in schizophrenia (Feifel et al., 2012a; Feifel et al., 2010b; Pedersen et al., 2011b), autism (Hollander et al., 2003) and have shown behavioural effects in patients with schizophrenia (Averbeck et al., 2011; Evans et al., 2011b), depression (Pincus et al., 2010), generalised anxiety disorder (Labuschagne et al., 2010, 2011) and autism (Guastella et al., 2010). Importantly, the prosocial effects of oxytocin may offer potential for synergistic pharmacotherapeutic and psychotherapeutic treatments of these severe disorders (Meyer-Lindenberg and Tost,

2012). One study demonstrating such potential benefits is a recent meta-analysis done in behavioural studies of clinical populations (Bakermans-Kranenburg and van, 2013). One advantage of oxytocin is that it is an endogenous hormone that has been used therapeutically in other areas of medicine, so its properties as a drug are fairly well known. In disorders such as psychosis, there is an increasing recognition that non-dopaminergic drugs are needed to advance care, and there exists great interest in alternative therapeutic targets to dopamine. There are currently no drug treatments available for social dysfunction, so the concept of a treatment for social ailments is very novel. Further studies are warranted to examine how oxytocin administration instantiates these behavioural changes in these groups and whether or not oxytocin administration produces the same pronounced effects over time.

CHAPTER 6 - THE NEURAL CORRELATES OF DECISION-MAKING DURING AN ASSOCIATIVE LEARNING TASK WITH A SOCIAL COMPONENT - THE EFFECTS OF OXYTOCIN ADMINISTRATION IN PATIENTS WITH SCHIZOPHRENIA

6.1 BACKGROUND

In addition to the standard diagnostic criteria of positive and negative symptoms, schizophrenia is generally accompanied by deficits in social cognition which are not currently treated by standard anti-psychotics (Penn et al., 2009; Sergi et al., 2007) despite being an important determinant of poor functional outcome (Couture et al., 2006; Fett et al., 2011). Deficits in social cognitive functioning in schizophrenia extend across multiple domains of social competence from difficulties in mental state attribution, and theory of mind (Bora et al., 2009; Brune, 2005b; Fett and Maat, 2011; Green, 1996), empathy (Shamay-Tsoory et al., 2007; Sparks et al., 2010), identifying emotional expressions (Huang et al., 2011; Kohler et al., 2003) to difficulties in maintaining eye gaze (Morris et al., 2009; Williams et al., 1999). Deficits in these social cognitive functions are particularly disabling as they have been shown to hinder the ability of patients with schizophrenia to interact with others and to integrate within society (Fett et al., 2011; Penn et al., 2000). Additionally, current treatment methods have little effect on improving social cognition. While psychosocial interventions have shown limited promise, these benefits have been narrow in their scope mainly improving isolated functions such as facial affect recognition and only showing limited improvements in theory of mind tasks (for a meta-analysis of studies see Kurtz and Richardson, 2011). Furthermore, current pharmacological interventions for the treatment of schizophrenia have no significant effect on improving social cognition (Gray and Roth, 2007). However, a promising new treatment, oxytocin has emerged which may help in alleviating these social cognition deficits in schizophrenia. Oxytocin

was originally known for its role in parturition and parental bonding (Insel and Young, 2001b). It has now been applied to exploring wider social benefits from looking at how oxytocin administration can improve levels of trust, without influencing risk-taking (Baumgartner et al., 2008; Kosfeld et al., 2005) to increasing the amount of time spent gazing at socially relevant regions of the face (Guastella et al., 2008) or even increasing ethnocentrism, or the cooperation between in-group members at the expense of out-group members (De Dreu, 2012; De Dreu et al., 2011).

The potential importance of oxytocin for the treatment of social cognitive impairment in patients comes from different lines of research. As the research is currently limited in scope, all known studies exploring the relationship between schizophrenia and its symptoms to oxytocin will be briefly overviewed. To start, research has shown that in patients with schizophrenia there is a relationship between oxytocin levels in both the plasma and cerebrospinal fluid (CSF) and social cognitive abilities as well with symptomatology measures such as positive and negative symptom scores. Additionally, a few studies have even shown that similar clinical traits to those found in schizophrenia which were observed in the healthy population also correlated with oxytocin measures (Tseng et al., 2014; Walss-Bass et al., 2013).

First, when looking at exogenous levels of oxytocin – measured in the CSF – conflicting results have been found when assessing whether or not oxytocin levels were lower in patients with schizophrenia than healthy controls (Beckmann et al., 1985; Glovinsky et al., 1994). However, in patients with schizophrenia, oxytocin levels in the CSF have been found to negatively correlate with the negative symptoms of the PANSS as well as second generation antipsychotic doses even when overall oxytocin levels did not differ from healthy controls (Sasayama et al., 2012b). It may be that differentiation

between healthy controls and patients with schizophrenia in terms of oxytocin levels in the CSF can only be quantified when other neurochemicals within the CSF are accounted for or if the symptoms in all patients assessed were significantly high. For example, it was only when oxytocin levels are entered into a model along with other substances in the CSF, multidimensional scaling modelling was able to correctly classify the CSF of patients with schizophrenia and healthy controls (Gattaz et al., 1985). Given that only one study, to the author's knowledge, has found general differences in oxytocin levels within the CSF between patients with schizophrenia and healthy controls (Beckmann et al., 1985), it appears that oxytocin levels may vary more closely with deficits in social cognition and other symptoms which are generally associated with schizophrenia.

Secondly, studies exploring endogenous, or peripheral/plasma levels, of oxytocin in patients with schizophrenia have found that oxytocin plasma levels correlated with various symptomatology measures in both schizophrenia and healthy controls. One study found that the avoidance of negatively valenced emotional faces positively correlated oxytocin levels and with positive and general symptoms as well as paranoia (Brown et al., 2014). Other research has also found that higher oxytocin plasma levels positively correlated with greater prosocial behaviours and, in females with schizophrenia, higher plasma levels of oxytocin also positively correlated with less severe positive symptoms and overall psychopathology (Rubin et al., 2010). A follow-up study by this group also found that oxytocin plasma levels in females (both controls and patients with schizophrenia), but not males, led them to perceive faces as happier (Rubin et al., 2011). These findings also extend to subgroups of schizophrenia patients and show that oxytocin may influence brain volume and endocrine production through

hypothalamic pituitary axis (HPA) functioning. One study looking at patients with schizophrenia with polydipsic hyponatremia, where increased fluid intake leads to an excess of fluid in the body causing dilution of sodium levels, showed that plasma oxytocin levels were lower in these patients as well as being inversely correlated with anterior hippocampal volume but not posterior hippocampal or amygdalar volume. Further correlations were also found between plasma oxytocin levels and hippocampal-mediated HPA functioning following stress responses as well as predicting the ability for patients to correctly identify facial expressions (Goldman et al., 2008) suggesting that, in some patients with schizophrenia, oxytocin also can be linked to functional and structural deficits. Further to this, a study using post mortem analysis of brains of patients with schizophrenia before medication, also found wide variation in morphometric values for structures which were assessed for oxytocin receptor distributions (Mai et al., 1993). Additionally, correlations have been observed when measuring behavioural interactions. A study done by Kéri et al. (2009) showed that oxytocin plasma levels were increased in healthy controls after a trust-related interaction but showed no difference in patients with schizophrenia. Further examination of the oxytocin plasma levels after the trust-based interaction revealed that low levels of oxytocin were related to negative symptoms but not positive symptoms, depression, anxiety and neuropsychological functions. These findings can be extended to apply toward explaining clinical characteristics within the healthy population as well. In both healthy controls and patients with schizophrenia, social cognitive capacity and social cognition bias, including attributional bias and jumping to conclusions, negatively correlated with plasma levels of oxytocin across genders who showed evidence for delusions based on the “unusual thought content” item of the brief psychiatric rating scale (Walss-Bass et al., 2013). Moreover, in healthy controls,

plasma levels of oxytocin were found to negatively correlate with schizoptypal personality scores in females but not males (Tseng et al., 2014). Overall, these studies show that oxytocin levels are more general indicators of symptoms severity in patients with schizophrenia and social cognitive ability such as facial affect recognition which extends to exploring variations in clinical features in the healthy population as well.

In addition to studies looking at oxytocin levels within the CSF and plasma, research has also shown that genetic variants in oxytocin receptor genes may be associated with schizophrenia and the symptoms associated with the illness. One study found that outcome specific to clozapine treatment response was predicted by oxytocin receptor gene expression as well as nominally correlating with negative symptoms (Souza et al., 2010). These findings have been supported by a study showing that, oxytocin receptor gene expression also correlated with PANSS negative and general symptom scores and age of onset as a predictor for empathic concern (Montag et al., 2012). Furthermore, a group of oxytocin receptor genes were found to predict the risk for schizophrenia (Montag et al., 2013). Together, these findings from exogenous and endogenous oxytocin levels, or plasma and CSF levels, as well as variations in oxytocin receptor gene expression suggest that lower levels of oxytocin are predictive of higher symptomatology associated with schizophrenia and deficits in social cognitive functioning such as facial affect identification. This supports the notion that altering oxytocin levels may have a positive effect on improving social cognitive abilities and symptomatology in patients with schizophrenia.

In light of these findings, a number of studies have currently been conducted to explore how oxytocin administration affects patients with schizophrenia. These studies investigated how both acute and longitudinal oxytocin administration affected a range

of behaviours in regard to improving symptomatology (Feifel et al., 2010a; Modabbernia et al., 2013; Pedersen et al., 2011a), social cognition (Davis et al., 2013; Woolley et al., 2014), verbal memory (Feifel et al., 2012b) and even improving olfactory discrimination (Lee et al., 2013).

Several studies to date have focussed on the long term effects of oxytocin treatment with respect to the reduction of symptomatology and improvement in social cognitive functioning (Davis et al., 2013; Feifel et al., 2012b; Feifel et al., 2010a; Gibson et al., 2014; Lee et al., 2013; Modabbernia et al., 2013; Pedersen et al., 2011a). All studies but one have found a significant reduction in various symptom scores in patients with schizophrenia after two to eight weeks of oxytocin administration compared to a placebo (Feifel et al., 2010a; Gibson et al., 2014; Modabbernia et al., 2013; Pedersen et al., 2011a). However, the results differed with respect to the symptom domains, some studies found reductions in positive symptoms but not negative symptoms and others found reductions in negative symptoms but not positive symptoms. Only one study, which used half the dose as the other studies (20 IU), found that oxytocin treatment improved olfactory discrimination but only had an effect on symptom scores in a particular subgroup of inpatients but not outpatients in reducing negative symptoms (Lee et al., 2013). The lack of other significant findings across all groups in this study may be attributable a number of factors including the low dosage and that the study may not have looked at treatment effects far enough out as other studies suggested periods of up to 6 weeks to reach an effect (Modabbernia et al., 2013). It may also show that inpatients are more sensitive to treatment effects. However, a meta-analysis of studies on the effect of oxytocin treatment on symptoms (with the exception of (Gibson et al., 2014)) found a modest effect size of treatment across

positive, negative and general symptoms (d = 0.52) (Gumley et al., 2014). Furthermore, one study also found that longitudinal oxytocin treatment over three weeks helped improve some theory of mind processing in patients with schizophrenia in addition to improving symptom scores (Pedersen et al., 2011a). This suggests that long term oxytocin administration may offer potential benefits for patients with schizophrenia for improving symptomatology as well as some aspects of social cognitive ability.

While these studies suggest that, over time, oxytocin may have an effect on symptomatology in schizophrenia, other studies have also explored the acute effects of oxytocin administration on general social cognition. Given that studies in healthy controls have shown changes in behavioural and neural activity after oxytocin administration (Wigton et al.), ranging from tasks looking at trust (Baumgartner et al., 2008) to exploring ingroup outgroup dynamics (De Dreu, 2012; De Dreu et al., 2011). These findings inspired similar studies in patients with schizophrenia. These studies have shown that oxytocin administration increases the ability of patients with schizophrenia to accurately identify emotions (Averbeck et al., 2012) as well as elevating the degree of empathy that patients with schizophrenia show toward an in-group (Abu-Akel et al., 2014). Although a few studies have shown that oxytocin administration is capable of improving emotion perception, this finding has not always been replicated. In one study, acute oxytocin administration was found to significantly improve "controlled social cognition," or how indirectly expressed social stimuli such as emotions, thoughts, intentions and complex deliberations are understood over longer periods of time, similar to theory of mind tasks, but not "automatic social cognition," or how social cues from the voice, face and body are interpreted, for example, explicit emotion recognition (Woolley et al., 2014). However, together, these

studies suggest that, even after an acute dose, oxytocin administration may help improve both basic and complex social cognitive processed in patients with schizophrenia.

To date, the working mechanisms of oxytocin and its effects on neural activity are not entirely clear. Imaging studies done in healthy controls tentatively suggests that it elicits a general attenuation of neural activity in social processing regions such as the amygdala. However, it is important to note that there may be a gender difference where oxytocin generally attenuates neural activity within the amygdala in male subjects (Wigton et al.; Zink and Meyer-Lindenberg, 2012), and augments neural activity in the amygdala in females (Domes et al., 2010). Unfortunately, gender differences in how oxytocin administration affects both behaviour and neural activity are currently underexplored. To date, no published studies have explored the effect of oxytocin administration on neural activity in patients with schizophrenia. However, previous work done in our group has shown that both patients with schizophrenia and healthy controls show a heightened aversion toward angry faces in an associative learning decision-making task incorporating social faces (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2011b; Furl et al., 2012), chapter 3 (page 73), 4 (page 119). In healthy controls, this bias was mitigated by oxytocin administration so that they were less averse toward choosing the angry face (Evans et al., 2010). One suggestion for the initial heightened aversion toward angry faces is that it is driven by amygdala hyperactivity, possibly due to an aberrant mesolimbic dopaminergic pathway (Rosenfeld et al., 2011). Given dopamine's role in the manifestation and treatment of schizophrenia which was explored in further detail in the earlier chapters, exploring the ties between oxytocin and dopamine and their combined effect on

patients with schizophrenia's social cognition and symptomatology would be beneficial in elucidating its treatment potential. As both dopamine and oxytocin have demonstrated relationships with the symptomatology of schizophrenia, a model of oxytocin, dopamine was proposed by Rosenfeld et al. (2011). Their model suggests that the amygdala plays a crucial role in facilitating social cognition in schizophrenia by modulating social salience through oxytocinergic and dopaminergic signalling. Imaging studies to date have shown, that at least in male healthy controls, oxytocin appears to attenuate neural activity in the amygdala which is believed to result in the facilitation of prosocial behaviours such as increased trust (Baumgartner et al., 2008) or emotion recognition (Gamer et al., 2010b). These studies suggest that using oxytocin to modulate neural activity within the amygdala could have a beneficial role in facilitating these same prosocial behaviours in patients with schizophrenia.

This chapter describes a study that utilised the same task described in the previous chapters to assess how acute oxytocin administration influences how subjects make decisions on value and facial valence. During this task, subjects were required to determine through trial and error which of two emotional faces (e.g. a happy and an angry face) is rewarded more often and select the optimal choice. Previously, the emotional information contained in the face stimuli has been found to influence task performance, with subjects demonstrating a bias towards the selection of happy faces over angry faces (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2011b; Furl et al., 2012) (Chapter 3 (page 73) and Chapter 4 (page 119)), and oxytocin administration has been found to mitigate this bias in healthy controls (Evans et al., 2010).

Given these findings, I hypothesise that:

1. Patients with schizophrenia will show the previously demonstrated bias toward picking the happy face even when the evidence supports the angry face as the best choice and they will not be biased toward picking either of the neutral faces. Furthermore, I hypothesise that the administration of oxytocin will act to attenuate the bias toward the happy face in the emotionally valenced condition.

2. Attenuation of bias when deciding between two emotionally valenced faces after oxytocin administration will be accompanied by a reduction of neural activity in regions associated with social processing such as the amygdala. This attenuation in neural activity will not be seen when patients are deciding between two neutral faces.

3. When processing reward prediction error, due to oxytocin's potential ties to the dopaminergic system and as oxytocin is believed to reduce the social salience of stimuli, neural activation correlating with RPE will be attenuated in response to oxytocin administration within areas rich in dopaminergic receptors such as the ventral striatum.

6.2 METHODS

6.2.1 PARTICIPANTS

Twenty right handed male patients with schizophrenia or schizoaffective disorder, diagnosed according to the ICD-10 (ICD-10, 1992) were included in this study. Patients were recruited as a subsample from those who had already taken part in the study from Chapter 4. Diagnoses were further confirmed through the independent

assessment of case notes. Intelligence quotient (IQ) was measured using the two-item Wechsler Abbreviated Scale of Intelligence (WASI) consisting of the vocabulary and matrix reasoning subtests (Wechsler, 1999). Demographic information can be found below in Table 6.1. All participants signed informed consent and were compensated for their participation in the study on completion of the testing. Ethical approval was obtained from the Camberwell and St. Giles Research Ethics Committee. Further details of recruitment and inclusion and exclusion criteria can be found in Chapter 2 (page 35).

TABLE 6.1 - Demographic and clinical sample characteristics

	Patients with schizophrenia *(N=20) (mean (SD))*
Age (years)	37.90 (7.43)
WASI IQ	98.85 (13.24)
NS-SeC	2.80 (1.70)
Gender	20M
Age at onset (years)	24.50 (6.48)
Duration of illness (years)	13.40 (6.53)
CPZ equivalents	430.05 (236.27)
PANSS	
Positive Symptoms	14.95 (4.97)
Negative Symptoms	18.30 (4.99)
General Symptoms	30.70 (7.10)
Total	63.95(14.65)

IQ = Intelligence quotient; M = Male; F = Female; SD = Standard deviation
WASI = Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999)
NS - SeC = National Statistics Socio-economic Classification (Rose, 2001)
CPZ = Chlorpromazine equivalent (Woods, 2003)
PANSS = Positive and Negative Symptom Scale (Kay et al., 1987)

6.2.2 TASK

The task used was a forced-choice, stochastically rewarded decision-making task incorporating faces of varying social valence. In each trial two faces were presented to the left and the right of the screen. Pairs consisted of either: a happy face and an angry face of the same identity, or of two neutral faces of differing identities. Each visit consisted of two scanning sessions comprised of four counterbalanced blocks of 30

trials each (Figure 2.5, page 47). Pairs of emotionally valenced stimuli (i.e. happy and angry faces) were alternated with pairs of neutrally valenced stimuli (i.e. neutral faces). Within each emotionally valenced block, the identities of each face were kept consistent but the order of presentation of each identity was counterbalanced across sessions. Each block consisted of 30 trials with the presentation of each face counterbalanced across the left and right sides. Probability estimates were assigned to the faces at the beginning of each trial such that on 60% of the trials one face would win and 40% of trials the other face would win. The probability distribution of each face winning was counterbalanced across blocks such that the angry face won more in half of the blocks and the happy face won more in the other half, and that identity one won more over identity two for half of the blocks and vice versa for both the emotionally valenced and neutral faces. The order of these wins was counterbalanced across the participants and visits. In each trial, participants were instructed to pick the face which, at that time, they believed was the most likely to win. They were told that after making this decision they would be told whether or not they had won where a win would show that they had won 10 pence along with their current winnings total and a loss was associated with no change in winnings and only the message "You lose." The presentation of stimuli is shown below in Figure 6.1. Further details, including the task instructions, can be found in Chapter 2 (page 44).

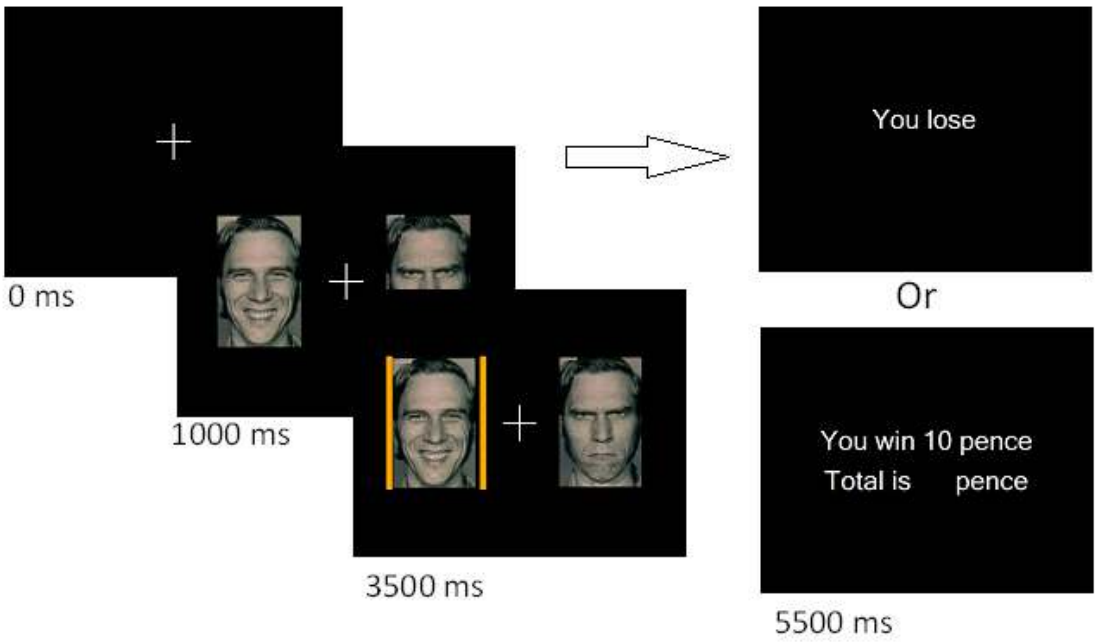

FIGURE 6.1 - Presentation of stimuli in the scanner for each trial

6.2.3 PHARMACOLOGICAL MANIPULATION

This study was a double blind crossover study administering oxytocin and placebo. Both the oxytocin (40 IU) and placebo nasal sprays were self-administered by our participants. First each spray was primed so that each spray delivered a full 4IU per nostril. Each participant was told to tilt their head back at a slight angle and insert the nasal spray into one of their nostrils while trying to keep the spray bottle as upright as possible. They were then told to push down on the pump action while simultaneously inhaling through their nostrils as deep as possible. They were then asked to switch nostrils and repeat this administration. A break of 45 seconds was given between each administration to allow for the nasal spray to be absorbed by the nostrils as recommended by (Guastella et al., 2013). Proper administration was demonstrated to each participant before self-administration albeit without physical insertion into the nostril and spraying of the agent. Each spray was acquired on the day of administration from the South London and Maudsley pharmacy, approximately one hour before being

administered to ensure an adequate storage temperature was not been breached before administration.

The timing of the oxytocin/placebo administration was designed to be given 45 minutes before the start of the first task within the fMRI scanner. This was set to be in line with previous fMRI studies which have shown significant changes in neural activity after oxytocin administration using this same time frame (Domes et al., 2007b; Kirsch et al., 2005; Kosfeld et al., 2005; Wittfoth-Schardt et al., 2012). However, the first task administered in the scanner was a trust-related decision-making task which does not form part of this thesis. The task used here was performed second after approximately 45 minutes of the trust-based task beginning approximately 90 minutes post-oxytocin/placebo administration.

6.2.4 FMRI DATA ACQUISITION

Functional magnetic resonance imaging (fMRI) data were acquired on a Discovery MR750 3T scanner at the Centre for Neuroimaging Sciences, London (T2* weighted gradient-echo echo-planar images (EPIs), repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, flip angle = 75°, 64 x 64 matrix, 24cm field of view). A 12-phase head coil array was used over the whole head for RF transmission and reception. Each whole-brain image contained 38 3-mm axial slices separated by a distance of 0.3 mm with in-plane isotropic voxel resolution of 3.75 x 3.75 mm. For each block, 430 scans were acquired and two sessions were recorded for each participant.

Before the experimental portion of the experiment, a T1-weighted structural scan using a fast-spoiled gradient-echo pulse sequence (TR = 9.356 ms, TE = 3.828 ms, flip angle = 12°, time to inversion = 450 ms) was acquired for reference purposes. The first four volumes were discarded to allow for transient effects.

Participants made their responses using a two buttons on a two button-box with their index and middle fingers of their right hand. Head movement was minimised using headphones and additional padding around the head and ears as well as around the arms and legs.

6.2.5 ANALYSIS

All data were preprocessed and analysed using Statistical Parametric Mapping 12 (SPM12) (Wellcome Department of Imaging Neuroscience, London, UK. www.fil.ion.ucl.ac.uk/spm) and MATLAB R2014a (MathWorks Inc. Sherbon, MA, USA). Further details of these steps can be found in Chapter 2 (page 53).

A general linear model (GLM) was constructed in SPM12 to analyse the images with each event modelled as a delta (stick) function. Each block, consisting of 30 trials, was modelled independently and was defined as being either a block using emotionally valenced faces (e.g. happy and angry faces) or neutral faces (e.g. two faces of different identities). Events of interest within each block included the presentation of the faces, a decision-making regressor indicating when the decision was made for which face the subject believed would be rewarded (determined by a button press), and the feedback presentation within each trial. Also modelled were regressors to represent the motion parameters as well as parametric modulators on the decision-making regressor for the probability of each face chosen being associated with a win and feedback regressors. The probability that the face they picked would win was calculated using an ideal observer. The calculations used to determine this probability are outlined in depth in Chapter 2 (page 47). The feedback regressor, associated with when they were given feedback about whether or not the face they had chosen was associated with a reward, was parametrically modulated by the reward prediction error (RPE)

determined by subtracting the actual reward (i.e. 1 for a win and 0 for a loss) from the predicted probability that the chosen face would win as detailed in Chapter 2 (page 49). Each regressor, except for the motion parameters, was convolved with a canonical hemodynamic response function and its temporal derivative. Missed trials were not modelled as events. Blocks where subjects failed to respond for greater than 50% of the trials were excluded from analysis as they were deemed to be insufficiently attending to the task. Furthermore, without feedback from all trials, it would have been more difficult for subjects to accurately assess which face was winning more often throughout the block. These excluded blocks accounted for one block across one subject after taking oxytocin when making decisions between two emotionally valenced faces.

Performance estimates were calculated across all trials by comparing the face the subject picked to the face the ideal observer assigned the highest probability of winning. In the case that both faces had equal probability of winning (i.e. at 50% probability) either face picked was deemed optimal. Overall performance estimates were calculated across all trials as the number of times the participant picked the face deemed optimal over the number of valid trials (i.e. 30 – any misses). These estimates were then averaged across all blocks which were not excluded to get an overall performance estimate for all blocks using emotionally valenced and neutral faces.

To assess how facial expression biased decision-making, all trials were separated into when participants agreed with the ideal observer and when they disagreed with the ideal observer for each facial valence as well as for the two neutral face identities. A 2x2 contingency table was calculated for each block type (i.e. emotionally valenced and neutral) representing choices by the ideal observer and choices by the participant.

When the probability for each face winning was ambiguous (i.e. equal probabilities for both faces), the contingency count for each face was increased by 0.5. Using this table it was possible to calculate the conditional probability of each participant choosing the happy face when they should have chosen the angry face given the current evidence for the angry face *p*(happy|angry) as well as when they chose the angry face when they should have chosen the happy face given the current evidence for the happy face *p*(angry|happy). The difference between these two measures was calculated to represent the degree of bias toward picking the happy face (*p*(happy|angry) – *p*(angry|happy)). This measure indicates how often participants ignore the evidence that has accumulated for the negatively valenced face and chose the positively valenced face compared to how often they ignored evidence that had accrued for the positively valenced face and chose the negatively valenced face. This bias distribution was examined across all participants and entered into a one sample t-test to see if it significantly differed from 0. It is important to note these conditional probabilities were calculated separately to the probability that each face would win. A more comprehensive overview with equations is provided in Chapter 2 (page 49). This process has been replicated in multiple studies to represent the degree of bias (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2010; Evans et al., 2011b; Furl et al., 2012).

The main focus of this study was to look at how decision-making and RPE affected neural activity so contrasts were looked at representing neural activity when a button was pressed to indicate which face the participant had chosen on a given trial, here after referred to as the decision-making condition as well as contrasts representing neural activity correlating with RPE given by the parametric modulator on reward

feedback. Second-level contrasts between drug conditions were assessed using paired sample t-tests. Within each drug comparison (i.e. oxytocin versus placebo), the main effect of task was analysed looking at by combining the blocks for emotionally valenced and neutral faces. Then contrasts were also created for blocks looking at only decision-making between the emotionally valenced faces to assess differences in decision-making with emotionally salient stimuli as well as within only the blocks looking at decision-making between neutral faces to assess differences in decision-making between general social stimuli with no emotional salience. Interaction effects between the emotion and drug were also analysed to see if there was any interaction between the emotionally valenced face condition and the neutral face condition and the drug they were administered.

To look at interaction effects between drugs and emotion an overall examination of blocks looking at the effects of drug (i.e. oxytocin versus placebo) and emotion (i.e. emotionally valenced versus neutral faces) were entered into 2x2 full factorial in SPM12 with drug and emotion as conditions.

Contrasts were whole brain cluster-level family wise error (FWE) corrected at $p<.05$ with a height threshold of $p < .005$, uncorrected, and an extent threshold of 100 contiguous voxels. Voxels which survived peak level FWE correction at $p<.05$ are also reported. Reported voxel coordinates were converted from Montreal Neurological Institute (mni) coordinates into Talairach coordinates using the function icbm_spm2tal (Laird et al., 2010; Lancaster et al., 2007a) and were entered into Talairach Daemon to confirm their location in gray matter (Lancaster et al., 1997; Lancaster et al., 2000). Questionable results were further visualised by entering the original mni coordinates into xjview (http://www.alivelearn.net/xjview). Results are reported as their original

mni coordinates as output by SPM12. If more than one voxel was found to be significant within a region without *a priori* interest, only the peak voxel is reported. Additionally, the contrast estimates from each image were analysed at the peak voxels to determine the direction of change between each condition analysed as significant decreases within one condition could still appear as increases in another condition even if no change in neural activity was present.

Region of interest analyses were also carried out within regions with an *a priori* interest to our study using small volume correction (SVC) within SPM12. Volumes of interest were defined using WFU PickAtlas Tool (Maldjian et al., 2003) for the amygdala and striatum and the ventral striatum was taken from Mawlawi et al. (2001). Only voxels which survived FWE correction at a peak level of $p < .05$ are reported.

Correlation analyses were carried out to compare the degree of mean neural activation within the ventral striatum mask defined above when looking at RPE compared with all PANSS scores as well as medication equivalents. A secondary analysis also looked to see if any correlations could be accounted for by the performance measures or the degree of bias in each patient. For correlation measures, all parameters were assessed for appropriate skew and kurtosis. For any variables which were not normally distributed, non-parametric measurements are reported as Spearman's rho. All other correlation measures are reported as Pearson *r* correlations. Significant values were reported for analyses that survived $p < 0.05$.

6.3 RESULTS

6.3.1 BEHAVIOURAL ANALYSIS

6.3.1.1 PERFORMANCE

To assess performance, in terms of the percentage accordance to an optimal observer, the face picked by the subject on each trial was compared to an ideal observer calculated based on the number of times a face won or would have won over the number of valid trials. Performance estimates across subjects were averaged separately across all neutral trials and emotional trials and are shown in Table 6.2. On average, patients with schizophrenia performed above chance levels (p>0.05). Furthermore, when choices were compared to an ideal observer, patients with schizophrenia did not significantly differ in their performance between the placebo and oxytocin conditions (p > 0.05).

TABLE 6.2 - Performance estimates referenced to an ideal observer in terms of percentage agreement

	Emotional faces	**Neutral faces**	**Difference from Chance (50%)**	
	mean (SD)	*mean (SD)*	*Emotional*	*Neutral*
Placebo	58.7% (11.2%)	62.7% (13.6%)	t(19) = 3.46, p = 0.003	t(19) = 4.19, p < 0.001
Oxytocin	61.4% (12.0%)	62.8% (14.9%)	t(19) = 4.22, p < 0.001	t(19) = 3.85, p = 0.001
Total	60.1% (11.6%)	62.3% (14.3%)		

* = p < 0.05; † p < 0.1, SD = Standard deviation

Performance was measured in terms of percentage accordance to an ideal observer (page 47). This was looked at separately across all blocks using emotionally valenced faces and neutral faces and t-values were calculated to show significant difference from chance

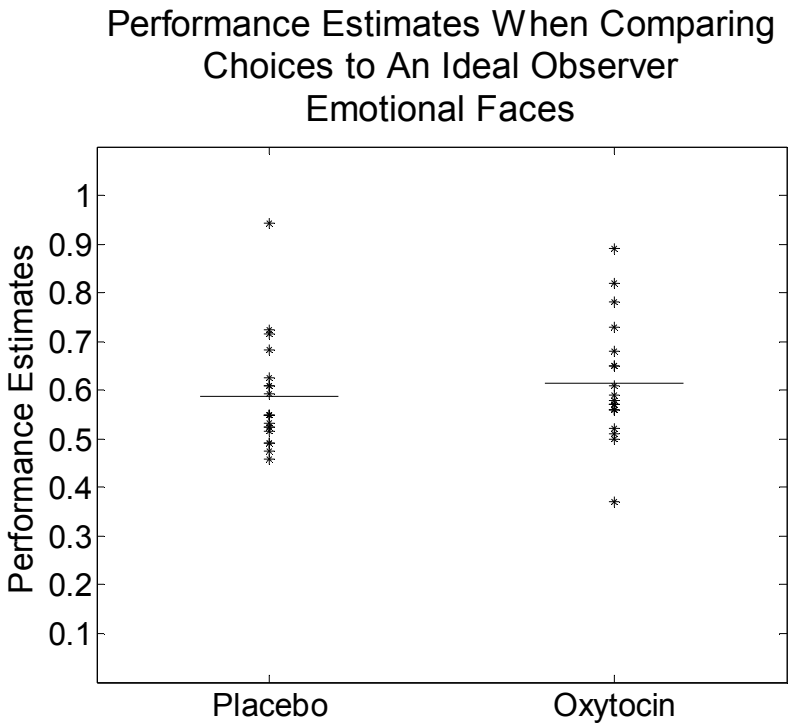

FIGURE 6.2 - Performance estimates for placebo and oxytocin when deciding between emotionally valenced faces where performance is compared to an ideal observer on a trial by trial basis. Each cross represents the performance of a single individual and the line represents the mean across all subjects.

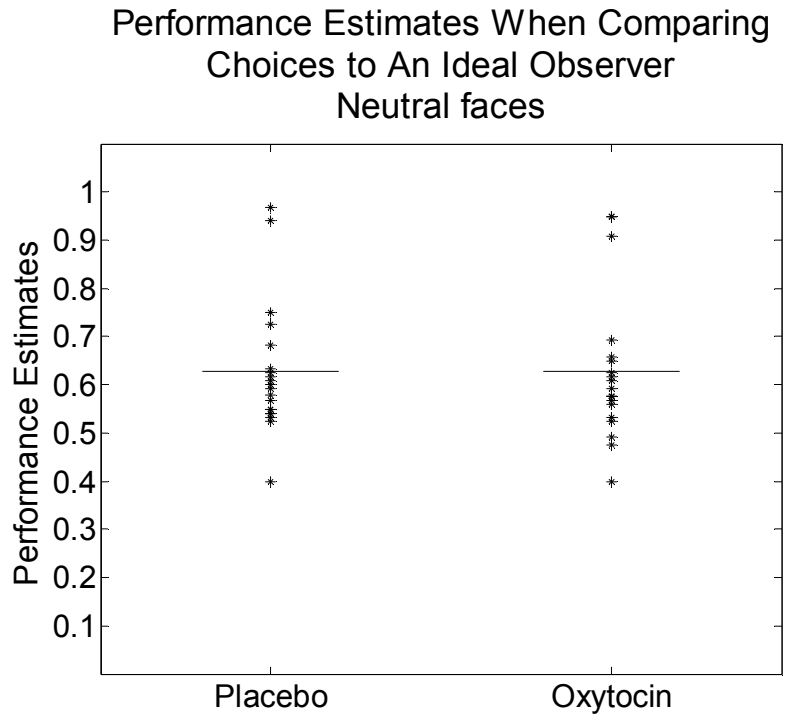

FIGURE 6.3 - Performance estimates for placebo and oxytocin when deciding between neutral faces where performance is compared to an ideal observer on a trial by trial basis. Each cross represents the performance of a single individual and the line represents the mean across all subjects

6.3.1.2 BIAS MEASURES

In accordance with our findings in the previous chapter, the distribution of bias toward picking the happy face was found to be significantly different from zero in the patients with schizophrenia in the placebo condition. However, after oxytocin administration, this bias was completely attenuated. Also, in accordance with our findings in the previous chapter, there was no bias toward picking either of the neutral identities in patients with schizophrenia after being administered placebo or oxytocin (Table 6.3).

TABLE 6.3 - Bias estimates toward a happy face and a neutral identity and their significance levels

	Emotional faces	**Neutral faces**	**Bias significance**	
	mean (SD)	*mean (SD)*	*Emotional faces*	*Neutral faces*
Placebo	0.14 (0.22)	0.02 (0.12)	t(19) = 2.82, p = 0.011*	t(19) = 0.88, p = 0.388
Oxytocin	0.06 (0.20)	-0.02 (0.13)	t(19) = 1.25, p = 0.225	t(19) = 0.85, p = 0.407

* significant at $p < 0.05$; SD = Standard deviation
Bias estimates are estimated as the degree of bias toward picking one of the faces when the ideal observer supports the other face as the better option using a contingency table described on page 49.
Bias significance was calculated as the difference from 0

6.3.2 FMRI ANALYSIS

6.3.2.1 NEURAL ACTIVITY DURING DECISION-MAKING

6.3.2.1.1 DECISION-MAKING ACROSS EMOTIONALLY VALENCED AND NEUTRAL FACES

6.3.2.1.1.1 WHOLE BRAIN ANALYSIS (MAIN EFFECT OF DRUG)

When looking at decision-making across both the emotionally valenced and neutral faces condition, no differences were observed between the oxytocin and placebo condition at a whole brain level.

6.3.2.1.1.2 REGION OF INTEREST ANALYSIS

As the amygdala is an important region for emotional processing and it has been shown that oxytocin administration has an effect on this region (Wigton et al., in

press), a region of interest (ROI) analysis was performed using small volume correction (SVC) within a mask for the left and right amygdala. No differences were observed between the oxytocin and placebo condition using SVC.

6.3.2.1.2 DECISION-MAKING BETWEEN EMOTIONALLY VALENCED FACES

6.3.2.1.2.1 WHOLE BRAIN ANALYSIS (MAIN EFFECT OF DRUG)

When looking at how decision-making affected neural activity in patients with schizophrenia after they had taken placebo versus oxytocin, whole brain analysis revealed significant clusters of neural activity in the bilateral precuneus extending into the right cuneus, posterior cingulate, left cingulate gyrus and bilateral temporal gyrus as well as the right insula. These regions also showed overlap with the temporoparietal junction (TPJ) bilaterally, whereby the cluster appeared to follow the borders of both the parietal and temporal lobes (Figure 6.4 and Table 6.4). Further analysis showed that this effect was driven by an attenuation of neural activity after oxytocin administration and an increase in neural activity after being administered placebo.

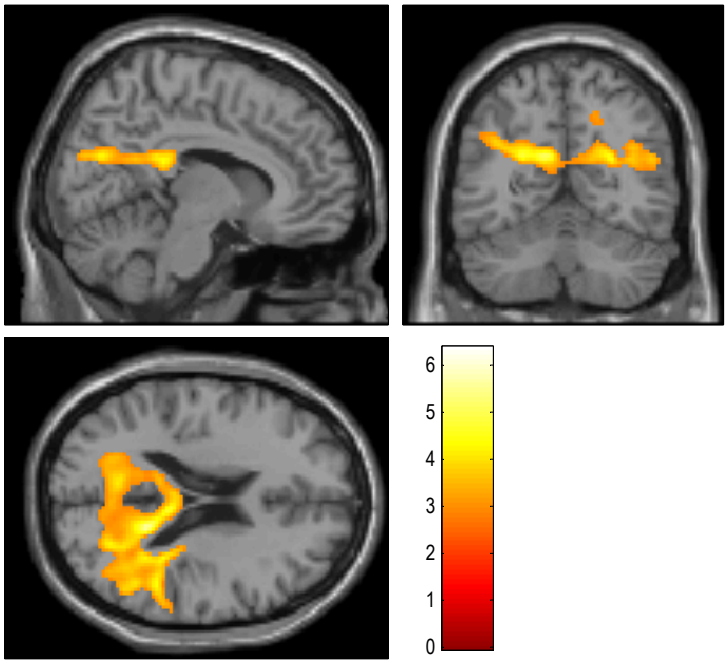

FIGURE 6.4 - Neural activity for decision-making between emotionally valenced faces for oxytocin administration versus placebo.This image shows that after taking

oxytocin, patients with schizophrenia demonstrated attenuated levels of neural activity from the bilateral precuneus along the bilateral TPJ than after taking a placebo. This image is shown at an uncorrected height threshold of $p < 0.005$ with an extent threshold of 100 and only clusters surviving FWE cluster-level correction of $p < 0.05$

6.3.2.1.2.2 REGION OF INTEREST ANALYSIS

A region of interest (ROI) analysis was performed using small volume correction (SVC) within a mask for the left and right amygdala. The results showed significantly more neural activity in the placebo condition over the oxytocin condition in the left amygdala (x = -25, y = -4, z = -14, t(38) = 4.89, p = 0.002, k = 52, FWE peak level corrected for SVC) (Figure 6.5). The right amygdala was also found to be significantly more active in the placebo condition over the oxytocin condition (x = 27, y = -8, z = -14, t(38) = 3.74, p = 0.020, k = 11, FWE peak level corrected for SVC) (Figure 6.5). Further analysis of these effects showed that they were driven by a stronger attenuation of neural activity in the amygdala after oxytocin administration and a slight increase in activity after placebo administration.

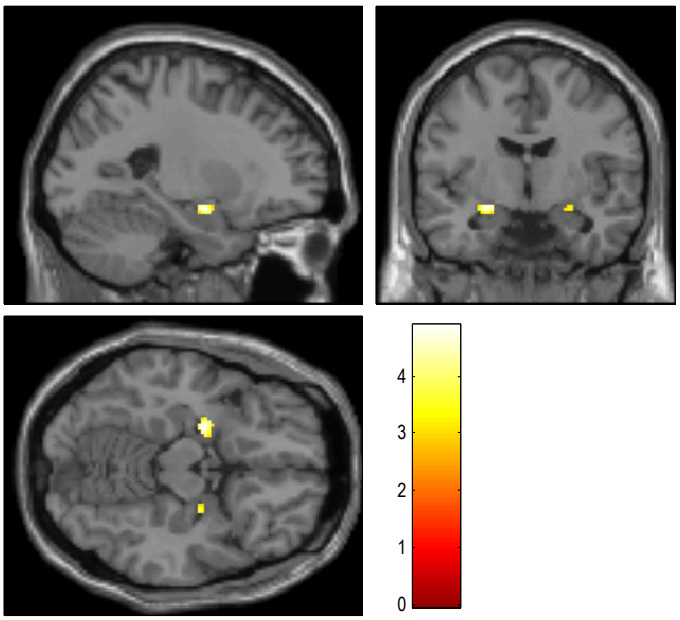

FIGURE 6.5 - Neural activity for decision-making between emotionally valenced faces for oxytocin administration versus placebo within the amygdala.This image shows that after taking oxytocin, patients with schizophrenia demonstrated attenuated levels of neural activity within the bilateral amygdala than after taking a placebo.

This image is shown at an uncorrected height threshold of $p < 0.005$ with areas surviving FWE peak-level correction of $p < 0.05$

6.3.2.1.3 DECISION-MAKING BETWEEN NEUTRAL FACES

6.3.2.1.3.1 WHOLE BRAIN ANALYSIS (MAIN EFFECT OF DRUG)

No differences in neural activity were found between the oxytocin and placebo condition when patients with schizophrenia were deciding between neutrally valenced faces.

6.3.2.1.3.2 REGION OF INTEREST ANALYSIS

Similarly, no differences in neural activity were found in the left or right amygdala between the oxytocin and placebo condition even after using SVC within this ROI.

6.3.2.1.4 INTERACTION EFFECTS FOR DECISION-MAKING BETWEEN EMOTIONALLY VALENCED AND NEUTRAL FACES

6.3.2.1.4.1 WHOLE BRAIN ANALYSIS (MAIN EFFECT OF DRUG)

When looking across the whole brain for an interaction effect of drug (i.e. oxytocin or placebo) by emotion (i.e. emotionally valenced versus neutral faces), similar effects to those observed in the condition where patients were deciding between the two emotionally valenced faces were found in the bilateral cuneus, and precuneus extending into the bilateral superior and middle temporal gyri, posterior cingulate, left cingulate gyrus, and right insula also extending across the TPJ bilaterally (Table 6.4 and Figure 6.6).

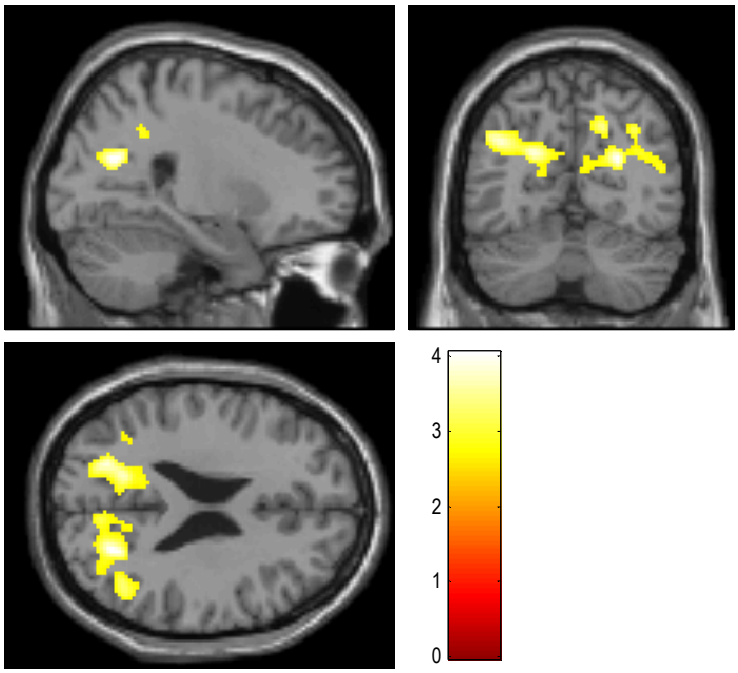

FIGURE 6.6 - Neural activity for interaction effects during decision-making between emotion and drug.This image shows that after taking oxytocin, patients with schizophrenia demonstrate greater levels of neural activity from the bilateral precuneus along the bilateral TPJ than after taking a placebo in the emotionally valenced condition but also that they show a slight increase in neural activity in these regions when deciding between two neutral faces after being administered oxytocin. This image is shown at an uncorrected height threshold of $p < 0.005$ with an extent threshold of 100 with only clusters surviving FWE cluster-level correction of $p < 0.05$

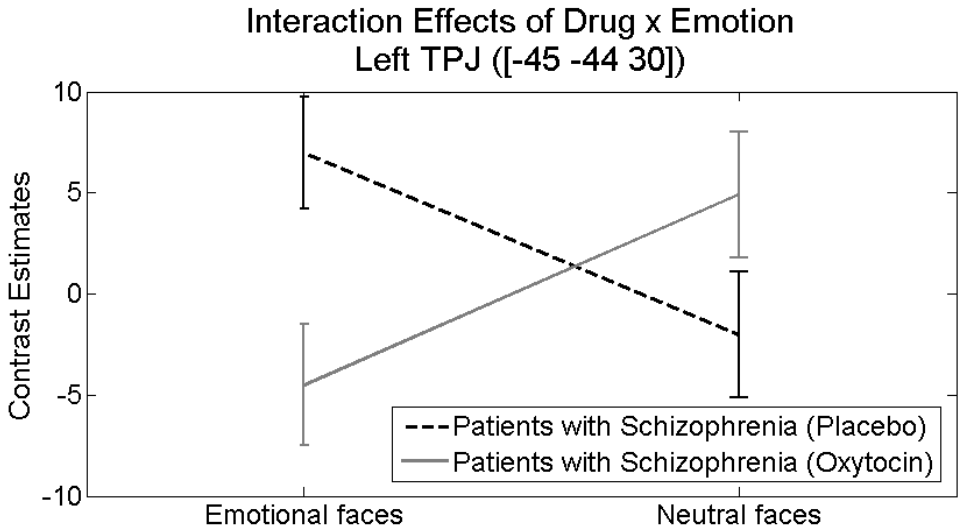

FIGURE 6.7 - Contrast estimates left TPJ looking at interaction effects between drug and emotion showing how oxytocin attenuated neural activity in the left TPJ for emotionally valenced faces but slightly augments neural activity when deciding between neutral faces. Contrast estimates and standard error estimates were taken from SPM.

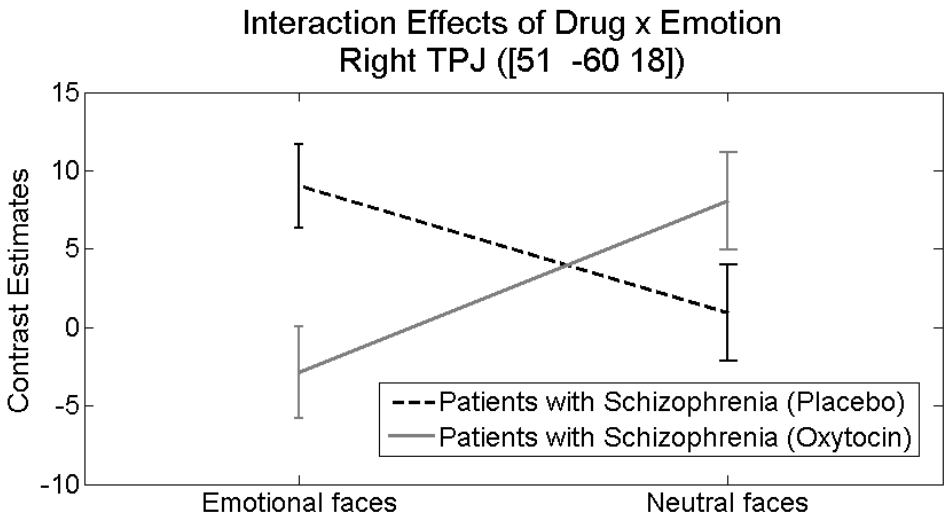

FIGURE 6.8 - Contrast estimates right TPJ looking at interaction effects between drug and emotion showing how oxytocin attenuated neural activity in the right TPJ for emotionally valenced faces but slightly augments neural activity when deciding between neutral faces. Contrast estimates and standard error estimates were taken from SPM.

6.3.2.1.4.2 REGION OF INTEREST

Using an ROI analysis, the left amygdala shows a trend toward significantly more neural activity in the placebo condition over the oxytocin condition (x = -21, y = -6, z = -12, t(76) = 2.81, p = 0.051, k = 3, FWE peak level corrected for SVC) (Figure 6.5)

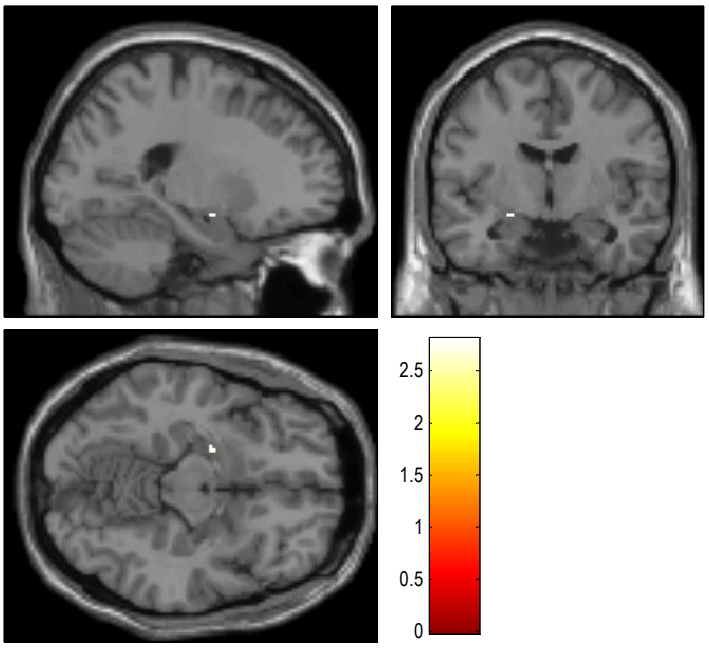

FIGURE 6.9 - Neural activity for interaction effects at a trend level between drug and emotion during decision-making within the left amygdala.This image shows an interaction effect at a trend level between drug and emotion within the left amygdala. This image is shown at an uncorrected height threshold of $p < 0.005$ with areas surviving FWE peak-level correction of $p < 0.1$

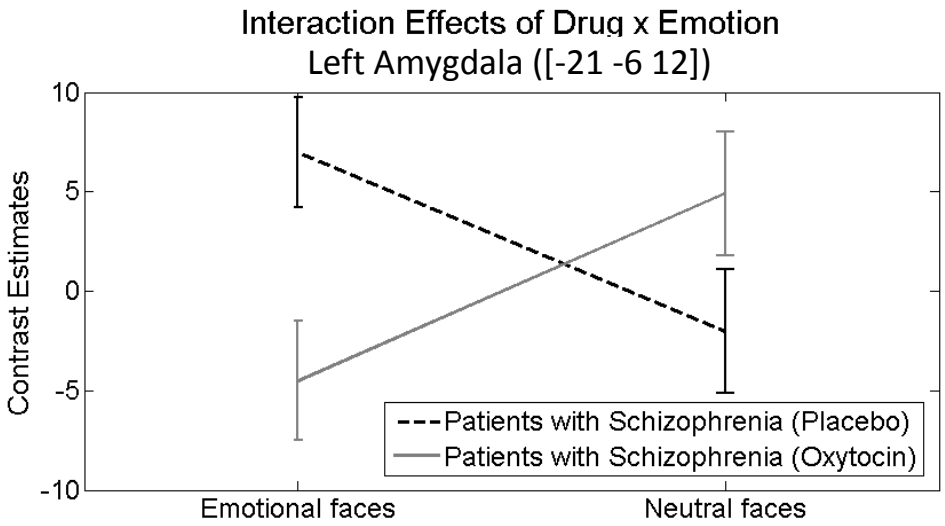

FIGURE 6.10 - Contrast estimates within a region of interest analysis around the left amygdala looking at interaction effects between emotion and drug showing that neural activity appears to be driven by a strong attenuation of the left amygdala by oxytocin when deciding between two emotionally valenced faced but not two neutral faces. Contrast estimates and standard error estimates were taken from SPM.

TABLE 6.4 - Neural correlates for decision-making in patients with schizophrenia for oxytocin versus placebo

Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
	Placebo > Oxytocin (Decision-making between Emotionally valenced faces)									
R	Posterior Cingulate	29	17	-48	22	6.39	<.001	<.001	4360	2.07
R	Posterior Cingulate	31	25	-66	22	4.67	<.001	<.001	4360	1.52
R	Posterior Cingulate	23	7	-34	20	4.62	<.001	<.001	4360	1.50
R	Posterior Cingulate	31	25	-60	24	4.41	<.001	<.001	4360	1.43
L	Posterior Cingulate	31	-23	-60	24	4.73	<.001	<.001	4360	1.53
L	Posterior Cingulate	31	-29	-66	26	4.20	<.001	<.001	4360	1.36
R	Cingulate Gyrus	31	21	-36	48	4.42	<.001	<.001	4360	1.43
L	Precuneus	31	-11	-62	24	5.04	<.001	<.001	4360	1.64
R	Precuneus	7	23	-52	44	4.50	<.001	<.001	4360	1.46
R	Precuneus	31	7	-70	24	4.25	<.001	<.001	4360	1.38
R	Insula	13	49	-40	20	4.25	<.001	<.001	4360	1.38
R	Insula	13	33	-36	20	4.25	<.001	<.001	4360	1.38
L	Middle Temporal Gyrus (TPJ)	39	-33	-66	28	4.24	<.001	<.001	4360	1.38
R	Superior Temporal Gyrus (TPJ)		59	-36	20	3.47	0.001	<.001	4360	1.13
L	Amygdala[a]		-25	-4	-14	4.89	<.001	0.002[a]	52	1.59
R	Amygdala[a]		27	-8	-14	3.74	0.001	0.020[a]	11	1.21
	Interaction effects (Drug (Oxytocin versus Placebo) x Emotion (Emotionally valenced faces versus Neutral faces)									
R	Precuneus	7	17	-60	40	3.87	<.001	0.019	1051	1.26
R	Precuneus	19	35	-64	40	3.19	0.001	0.019	1051	1.03
R	Precuneus	31	25	-50	38	2.89	0.002	0.019	1051	0.94

Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
R	Precuneus	23	9	-62	22	2.77	0.004	0.019	1051	0.90
R	Precuneus	31	37	-72	24	2.70	0.004	0.019	1051	0.88
L	Precuneus	31	-23	-68	26	4.02	<.001	0.002	1660	1.30
L	Precuneus	31	-19	-46	38	3.19	0.001	0.002	1660	1.03
R	Cuneus	18	7	-72	24	3.15	0.001	0.019	1051	1.02
R	Middle Temporal Gyrus (TPJ)	19	51	-60	18	3.60	<.001	0.019	1051	1.17
L	Middle Temporal Gyrus	39	-39	-62	32	3.80	<.001	0.002	1660	1.23
L	Superior Temporal Gyrus	39	-45	-54	34	3.62	<.001	0.002	1660	1.17
L	Superior Temporal Gyrus (TPJ)	13	-45	-44	30	3.41	0.001	0.002	1660	1.11
R	Posterior Cingulate	23	11	-58	22	2.76	0.004	0.019	1051	0.90
L	Posterior Cingulate	30	-17	-68	16	3.05	0.002	0.002	1660	0.99
L	Cingulate Gyrus	31	-19	-40	28	2.97	0.002	0.002	1660	0.96
L	Amygdala[b]		-21	-6	-12	2.81	0.003	0.051[b]	3	0.91

Corresponding coordinates for each brain region listed represent the peak voxels for each corresponding region within each significant cluster. All areas reported were found to be significant at a family wise error cluster level corrected threshold of <.05 after running a whole brain analysis at an uncorrected threshold of *p*<.005.

k = cluster size; BA = Brodmann's Area

Effect size was calculated using Cohen's d

a Regions which were found to be significant using small volume correction. FWE values are reported at peak level significance after correction

b Regions which were found to be significant at a trend level using small volume correction. FWE values are reported at peak level significance after correction

6.3.2.2 REWARD PREDICTION ERROR (RPE)

6.3.2.2.1 RPE ACROSS EMOTIONALLY VALENCED AND NEUTRAL FACES

6.3.2.2.1.1 WHOLE BRAIN ANALYSIS (MAIN EFFECT OF DRUG)

When looking at how RPE correlated with neural activity in patients with schizophrenia after placebo versus oxytocin administration across the emotionally and neutral valenced faces, whole brain analysis showed no significant areas of activation.

6.3.2.2.1.2 REGION OF INTEREST ANALYSIS

Using an ROI analysis with SVC within the ventral striatum no voxels were found to be more significant after placebo or oxytocin administration for RPE correlating with neural activity in the emotionally valenced and neutral face condition.

6.3.2.2.2 RPE FOR EMOTIONALLY VALENCED FACES

6.3.2.2.2.1 WHOLE BRAIN ANALYSIS (MAIN EFFECT OF DRUG)

When looking at how RPE correlated with neural activity in patients with schizophrenia across the emotionally valenced faces, whole brain analysis revealed a significant cluster of neural activity that was more active after patients with schizophrenia had taken placebo over oxytocin in the right superior parietal lobe, extending into the cuneus, inferior parietal lobe, supramarginal gyrus and superior temporal gyrus, with some voxels overlapping the right TPJ (Table 6.7 and Figure 6.11). It is important to note that similar neural activation was observed in the left hemisphere at this threshold; however, it did not survive the cluster extent criterion as not all the voxels were contiguous. Further analysis showed that the

significant neural activity observed was due to attenuation of neural activity after oxytocin administration and an increase in neural activity after placebo administration.

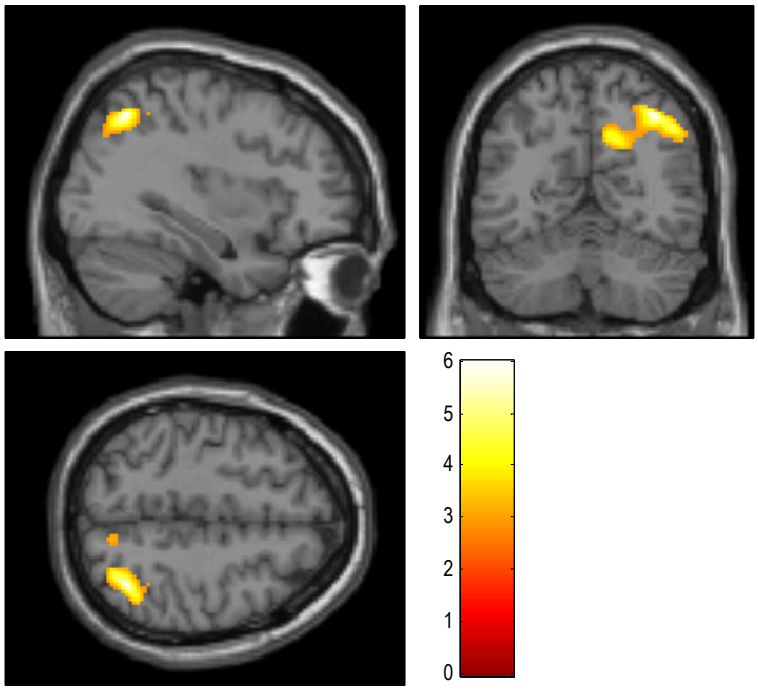

FIGURE 6.11 - Neural activity correlating with RPE when deciding between two emotionally valenced faceswhere greater neural activity was observed after placebo administration than oxytocin administration in the right cuneus extending to the right TPJ. This image is shown at an uncorrected height threshold of $p < 0.005$ with an extent threshold of 100 with only clusters surviving FWE cluster-level correction of $p < 0.05$

6.3.2.2.2.2 REGION OF INTEREST ANALYSIS

Using an ROI analysis with SVC within the ventral striatum no voxels were found to be more significant after placebo or oxytocin administration for RPE correlating with neural activity in the emotionally valenced face condition.

6.3.2.2.2.3 CORRELATION ANALYSIS FOR RPE IN EMOTIONALLLY VALENCED FACES

Mean neural activity for each subject was extracted from the ventral striatum and correlated with PANSS scores and chlorpromazine equivalents. No correlations were found between PANSS scores and CPZ equivalents and neural activation after placebo administration.

However, there was a significant positive correlation between neural activity in this region in response to oxytocin administration between all PANSS subscale and total scores (Table 6.5). Furthermore, when looking at the difference between neural activity after oxytocin administration over placebo administration, there was a positive correlation between positive and total PANSS scores as well as a negative correlation between CPZ equivalents and neural activation in the ventral striatum for RPE. These findings suggest that oxytocin has the largest effect on participants with high positive PANSS scores which may be slightly decreased by medication effects.

TABLE 6.5 - Correlation measures between neural activity for RPE within the ventral striatum while deciding between two emotionally valenced faces and clinical sample characteristics

	Oxytocin	Placebo	Difference (Oxytocin - Placebo)
PANSS (Positive Symptoms)	0.701, *p*= 0.001**	-0.046, *p* = 0.846	0.479, *p*= 0.033*
PANSS (Negative Symptoms)	0.452, *p* = 0.045*	-0.020, *p* = 0.934	0.301, *p*= 0.197
PANSS (Total)	0.596, *p*= 0.006**	-0.134, *p* = 0.572	0.483, *p* = 0.031*
CPZ Equivalents	-0.253, *p*= 0.281	0.359, *p* = 0.121	-0.448, *p* = 0.048*

*significant at $p < .05$; **significant at $p < .01$
Correlation measures are reported as Pearson *r* correlations. All values were assessed for skew and kurtosis.

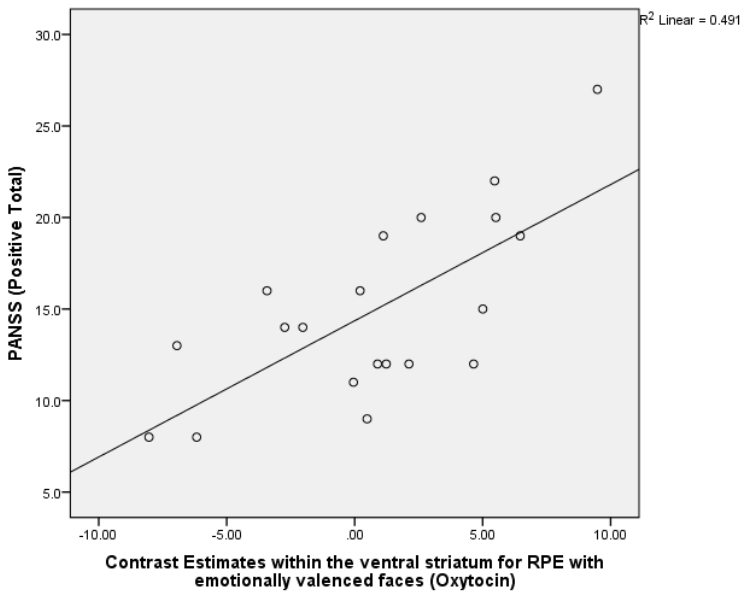

FIGURE 6.12 - Correlation measures between positive PANSS scores and contrast estimates for RPE within the ventral striatum after being administered oxytocin

6.3.2.2.3 RPE FOR NEUTRAL FACES

6.3.2.2.3.1 WHOLE BRAIN AND REGION OF INTEREST ANALYSIS

No differences were found in neural activity for RPE between oxytocin and placebo in the neutral condition at a whole brain level or after SVC.

6.3.2.2.3.2 CORRELATION ANALYSIS FOR RPE IN NEUTRAL FACES

Mean neural activity for each subject correlating with RPE in the neutral face condition was extracted from the ventral striatum and correlated with PANSS scores and CPZ equivalents. There was a significant positive correlation was found in response to the difference between oxytocin administration and placebo administration for total PANSS scores as well as CPZ equivalent measures. No other significant correlations were found between any other PANSS scores and neural activity after placebo and oxytocin administration separately (Table 6.6).

TABLE 6.6 - Correlation measures between neural activity within the ventral striatum for RPE while deciding between two neutral faces and clinical sample characteristics

	Oxytocin	**Placebo**	**Difference (Oxytocin - Placebo)**
	Correlation measures (*r*)		
PANSS (Positive Symptoms)	0.397, *p* = 0.083†	0.029, *p* = 0.903	0.303, *p*= 0.193
PANSS (Negative Symptoms)	0.067, *p* = 0.779	-0.036, *p* = 0.881	-0.396, *p*= 0.084†
PANSS (Total)	0.214, *p*= 0.364	-0.357, *p* = 0.123	0.449, *p* = 0.047*
CPZ Equivalents	-0.368, *p*= 0.111	0.246, *p* = 0.296	-0.490, *p* = 0.028*

*significant at $p < .05$; †trend level significance at $p < .1$
Correlation measures are reported as Pearson *r* correlations. All values were assessed for skew and kurtosis.

TABLE 6.7 - Neural activity for reward prediction error for placebo versus oxytocin

Side	Brain Regions	BA	x	y	z	t-score	p (uncorrected)	p(cluster FWE corrected)	k	effect size
Placebo>Oxytocin (RPE for Emotionally valenced faces)										
R	Superior Parietal Lobule	73	35	-60	50	5.99	<.001	0.004	1277	1.94
R	Superior Parietal Lobule	72	35	-48	50	2.89	0.005	0.004	1277	0.94
R	Inferior Parietal Lobule	40	45	-56	46	4.77	<.001	0.004	1277	1.55
R	Inferior Parietal Lobule	40	55	-52	40	3.70	0.001	0.004	1277	1.20
R	Cuneus	70	11	-64	38	5.76	<.001	0.004	1277	1.87
R	Precuneus	31	21	-56	38	4.16	<.001	0.004	1277	1.35
R	Precuneus	72	17	-66	52	3.04	0.003	0.004	1277	0.99
R	Supramarginal Gyrus (TPJ)	40	61	-50	38	3.71	0.001	0.004	1277	1.20
R	Superior Temporal Gyrus	39	43	-52	36	3.28	0.002	0.004	1277	1.06

Corresponding coordinates for each brain region listed represent the peak voxels for each corresponding region within each significant cluster. All areas reported were found to be significant at a family wise error cluster level corrected threshold of <.05 after running a whole brain analysis at an uncorrected threshold of *p*<.005; k = cluster size; BA = Brodmann's Area
Effect size was calculated using Cohen's d

6.4 DISCUSSION

This study explored the effect of oxytocin on decision-making in an associative learning task in patients with schizophrenia using emotionally valenced and neutral faces as social variables in order to assess how oxytocin administration may affect neural activity and emotional bias in patients with schizophrenia. Schizophrenia is associated with profound difficulties in social decision-making which are not currently treated by standard antipsychotics. As oxytocin has been demonstrated to positively impact on facilitating social cognition and facial recognition, it was used here to determine if it could also influence decision-making where social variables were secondary to the main decision-making task. It was found that oxytocin administration exerted similar positive prosocial effects in the patients with schizophrenia by attenuating bias toward choosing a happy face - or attenuation of the aversion toward an angry face - which was accompanied by the attenuation of neural activity in social regions including the amygdala and TPJ. Furthermore, the effects of oxytocin on RPE were found to positively correlate with neural activity in the ventral striatum and positive symptom scores suggesting that symptomatology in schizophrenia may undermine the effects of oxytocin administration on reward related activity. These findings demonstrate that oxytocin administration is capable of inducing a robust effect on neural activity in patients with schizophrenia with potentially beneficial prosocial effects.

After being administered a placebo, patients with schizophrenia demonstrated the same bias toward picking the happy face as shown in previous studies in both healthy participants and patients with schizophrenia (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2010; Evans et al., 2011b; Furl et al., 2012) and in chapters 3 and 4 (pages 73 and 119) despite performing the task significantly above chance. Thus,

when the evidence for being rewarded was greater for angry face, patients reliably chose the happy face more often resulting in a bias toward choosing the happy face. However, after being administered oxytocin, this bias toward the happy face was completely attenuated. This meant that patients with schizophrenia no longer showed an aversion toward picking the angry face nor did they show an affinity for choosing the happy face. As expected, no bias was found with respect to either of the neutral faces after being administered placebo or oxytocin. Furthermore, changes in bias attribution during decision-making were also accompanied by an attenuation of neural activity in the TPJ and amygdala after oxytocin administration compared to placebo administration. This attenuation was present in a cluster extending bilaterally from the precuneus into the bilateral TPJ. The TPJ is a brain region which has been found to show increased neural activation during social processing (Decety and Lamm, 2007) and generally shows diminished neural activity in schizophrenia compared to healthy controls during tasks involving mentalising (Das et al., 2012; Lee et al., 2011; Walter et al., 2009). The amygdala has been implicated in other oxytocin imaging studies as a region which generally is attenuated during tasks involving the processing of emotional faces in male subjects (Wigton et al.). A region of interest analysis using the amygdala also showed that oxytocin attenuated neural activity in the bilateral amygdala but that this effect was only significant during decision-making in the emotionally valenced condition and not during the neutral condition. Furthermore, although an interaction analysis of drug and emotion was significant suggesting that amygdala activity was also increased in the neutral face condition after oxytocin administration; further examination showed that these effects were driven by a greater difference in neural activity after oxytocin and placebo administration in the emotionally valenced condition than in the neutral condition suggesting that these effects are more specific

to oxytocin's effect on processing emotionally salient information. Attenuation of these social regions alongside the attenuation of bias in patients with schizophrenia is in-line with data from healthy subjects showing that attenuation of social regions may facilitate prosocial behaviour.

Previous studies exploring the effects of oxytocin administration on neural activity have shown that, in healthy males, relative to a placebo, oxytocin administration tends to attenuate neural activity in regions associated with social behaviour, such as the TPJ (Domes et al., 2007b; Frith and Frith, 2012; Wittfoth-Schardt et al., 2012) and amygdala (Domes et al., 2007b; Kirsch et al., 2005; Wigton et al.). Although mainly known for its role in mentalising, the TPJ has also been linked to other social processes including social attention (Asplund et al., 2010; Kucyi et al., 2012), detecting novel stimuli (Downar et al., 2000; McCarthy et al., 1997b) to increasing attention toward novel/salient stimuli (Castelli et al., 2002). Furthermore, the TPJ has also been associated with the severity of auditory hallucinations in schizophrenia (Gromann et al., 2012; Vercammen et al., 2010). The amygdala, moreover, also plays a role in emotional processing in the modulation of vigilance in the presence of stimuli signalling increased social novelty or threat (Phelps, 2006; Whalen et al., 1998) as well as in modulating neural activity in response to facial expressions (Anderson and Phelps, 2000). Activation in both the TPJ and amygdala was also attenuated by the administration of oxytocin, relative to a placebo, in healthy males, when processing novel faces over familiar faces (Wittfoth-Schardt et al., 2012) as well as when implicitly processing emotionally valenced faces over neutral faces (Domes et al., 2007a; Kirsch et al., 2005). Our findings suggest that this attenuation in neural activity in social regions in healthy controls can also be extended to patients with schizophrenia.

Furthermore, the attenuation of neural activity was accompanied by attenuation in the degree of bias that patients with schizophrenia displayed for choosing the happy face when the angry face was more likely to be rewarded such that neither face was preferred by the patients with schizophrenia after they had taken oxytocin. This is similar to the previous behavioural finding shown in healthy controls during this task after oxytocin administration (Evans et al., 2010). Consistent with this, oxytocin has been shown to slow identification of negatively valenced stimuli while enhancing the recognition of positively valenced stimuli (Di Simplicio et al., 2009) suggesting that the observed reduction in neural activity may be indicative of oxytocin administration acting to dampen this enhancement toward positively valenced social stimuli by decreasing the aversive aspects of negatively valenced social stimuli (Averbeck, 2010). In accordance with previous studies, the amygdala, TPJ and precuneus did not show any significant changes in neural activity due to oxytocin administration in the neutral condition (Domes et al., 2007b; Labuschagne et al., 2010) demonstrating that oxytocin administration only had a significant effect on neural activity in the processing of emotionally valenced stimuli.

Although patients with schizophrenia generally demonstrate hypoactivation of the TPJ during tasks involving mentalising (Das et al., 2012; Lee et al., 2011), it has been hypothesised that these decreases in neural activity may be due to the TPJ being more active while mentalising as patients may be attributing greater levels of intentionality to other parts of the task which are not social in lieu of only attributing social causality (Walter et al., 2009). Additionally, some studies have even shown hyperactivation in the TPJ during a mentalising task compared to healthy controls (Brüne et al., 2008). However, Chapter 4 (page 128) showed that patients with schizophrenia do not show

significant changes in neural activity than healthy controls during the task used in this thesis in the TPJ. Given that the group of patients analysed in the current chapter were a subset of patients from the previous experiment, this suggests that, during this task, neural activity within the TPJ for patients with schizophrenia is not significantly altered from that of healthy controls.

With respect to RPE, or the difference between expected and actual reward, oxytocin administration was found to attenuate neural activity in a more superior region of the bilateral precuneus extending into more superior regions of the TPJ than the region which showed an attenuation of neural activity in the decision-making condition. These effects were also found to only be significant for RPE in the emotionally valenced face condition. This finding suggests that attenuation of neural activity in social regions after oxytocin administration may not be solely constrained to the observation, or implicit processing, of social stimuli but may also extend to the processing of social and financial reward in patients with schizophrenia. This has also been suggested in previous work in healthy controls showing that oxytocin administration was able to increase sensitivity to social feedback relative to non-social feedback when comparing the differences in processing the intrinsic value of faces compared to the processing of abstract, non-social stimuli (Hurlemann et al., 2010) as well as other work showing an increase in neural activity in the TPJ for RPE in social learning (Behrens et al., 2008; Frith and Frith, 2012).

Although no significant differences between oxytocin and placebo were observed using SVC within the ventral striatum, an exploratory analysis was run to see if oxytocin had any general effects on neural activity within the ventral striatum and to see if these effects could be explained by symptomatology within the patients with

schizophrenia. When extracting for individual variance within the ventral striatum, the degree to which oxytocin increased neural activity positively correlated with all PANSS scores and RPE in the emotionally valenced faces, and when looking at correlations between the difference in neural activity from RPE in the emotionally valenced faces between oxytocin administration and placebo administration, this positive correlation is still significant for positive and total PANSS scores and also showed a negative correlation with chlorpromazine medication equivalents. These findings suggest that individuals with higher symptom profiles in schizophrenia, especially in regard to positive symptoms, show greater increases in neural activity after oxytocin administration in dopamine rich areas such as the ventral striatum and that antipsychotic medication may dampen the effects of oxytocin administration in the ventral striatum. Additionally, differences in neural activity correlating with RPE between oxytocin and placebo administration for neutral faces correlated with total PANSS scores and also negatively correlated with chlorpromazine medication equivalents, giving a potential indication of the general influence of oxytocin administration on RPE in relation to symptomatology scores. It is important to note that no high symptoms scores or medication equivalents, as measured under placebo administration, accounted for changes in neural activation in the ventral striatum. Correlations in these measures could have indicated that these correlations may have been a result of general extra striatal dopamine release due to symptom scores or an inhibition from medication effects (Abi-Dargham et al., 2000; Juckel et al., 2006). When taking into account the difference between neural activity after the oxytocin administration and placebo administration, these results demonstrate that oxytocin administration had the greatest effect on neural activity in participants with higher positive PANSS scores and that the effect of oxytocin administration may have been

diminished by medication effects. This is of clinical relevance as it suggests that patients who do not respond well to conventional treatments may respond to oxytocin administration.

Potentially more interesting is the finding that these observed neural effects are present so late after oxytocin administration. The timings of this study were set to maximise the effects of oxytocin administration on neural activity in line with the timings from current studies on one of the other tasks used in the scanner (exploring trust based interactions) which is not analysed here. This other trust-based task was designed to begin at approximately 45 minutes post- oxytocin or placebo administration and lasted approximately 45 minutes. Thus the task explored in this chapter was designed to begin around an hour and a half past the administration of oxytocin or a placebo. Only one study to date has looked at how intranasal oxytocin administration affects CSF and plasma oxytocin levels over time in order to determine its maximum effects on CSF and plasma concentration (Striepens et al., 2013). They found that, although plasma levels of oxytocin increased after 15 minutes, no significant increases in CSF oxytocin levels were observed until 75 minutes post administration. However, the sample size was extremely small (1 on placebo and 3 on oxytocin) and no further time points were recorded so it is hard to draw any firm conclusions on whether these findings would extend to a larger population and how long oxytocin in the CSF would remain elevated after their last time point. However, a similar study in humans using a related neuropeptide, vasopressin, which has formed the basis for the current timings used in many oxytocin imaging studies, showed that oxytocin levels were increased in the CSF compared to a placebo up to at least 2 hours after administration, after which no more measurements were taken (Born et al.,

2002). Even though plasma levels of oxytocin have not been found to correlate with levels in the CSF (Kagerbauer et al., 2013; Striepens et al., 2013), the literature suggests that oxytocin administration can result in elevated levels of plasma oxytocin for up to 7 hours, with oxytocin levels up to 10 times greater than in the placebo condition (van Ijzendoorn et al., 2012) and that, in rodents, CSF oxytocin levels are almost immediately elevated following intranasal administration and can remain elevated for up to 90 minutes in the amygdala and hippocampus (Neumann et al., 2013). Given that plasma oxytocin levels have been found to correlate with social behaviour these findings may still show that the effects of oxytocin administration are more prolonged than currently thought. Together, these findings highlight our lack of understanding in the time course of oxytocin administration on increasing the levels of oxytocin within the CSF and suggest that it takes longer than previously thought to increase oxytocin within the CSF. Our study indicates that, at least in patients with schizophrenia, the behavioural and neural effects of oxytocin persist at least up until almost two hours after administration and suggests this task began closer to the actual peak for oxytocin concentration in the CSF than previous work.

This current study only looked at patients with schizophrenia without examining a matched healthy control cohort therefore it is not currently possible to say how effects may compare to healthy controls and whether or not healthy controls would show attenuation in these regions to a greater or lesser degree, or not at all. However, as described in Chapter 4 (page 121), patients with schizophrenia did not show significant differences in neural activity to healthy controls in the same regions where oxytocin administration was found to attenuate neural activity, and given that oxytocin administration appears to attenuate neural activity in areas similar to those seen in

other studies with healthy controls, these findings are in line with what has been previously reported in a healthy population. This suggests that these findings were not due to general differences in neural activity between patients with schizophrenia and healthy controls but reflect a general attenuation of neural activity in social regions via oxytocin administration.

This study was double blinded and took every care to prevent participants from being able to determine which drug, placebo or oxytocin, they had received, as subjective differences in their experiences may have influenced the current results. However, throughout the study, only two participants reported feeling a difference between the two sessions. Furthermore, any changes in perception would still not account for the significant attenuations seen in neural activation seen across all patients with schizophrenia in addition to the behavioural changes observed.

Overall, these findings show that oxytocin is capable of attenuating neural activity in patients with schizophrenia in areas which are associated with social processing. These changes are accompanied by changes in bias attenuation indicative of increased prosocial behaviour. Furthermore, the effect of oxytocin administration on the reward processing during decision-making between two emotional faces positively correlated with positive symptoms in schizophrenia which suggests that patients with schizophrenia with higher positive symptoms may be more susceptible to the neural effects of oxytocin administration than others at least when processing social reward. Additionally, this indicates that oxytocin may not only influence the processing of social stimuli but the way in which social reward is processed.

CHAPTER 7 - GENERAL DISCUSSION

This thesis comprised two main experiments using functional Magnetic Resonance Imaging (fMRI) and the administration of different pharmacological probes to explore neural activity in healthy controls and patients with schizophrenia.

The objective was to explore the role of dopamine and oxytocin in socially-focused associative learning by comparing neural activity after dopaminergic perturbation in healthy controls to patients with schizophrenia, as well as by studying how oxytocin affects neural activity during socially-focused associative learning in patients with schizophrenia.

The main findings from this thesis showed that as demonstrated in previous studies, Chapters 3, 4 and 6 (pages 73, 119 and 218), when deciding between two emotionally valenced faces, healthy controls and patients with schizophrenia reliably favoured a happy face over an angry face even when the angry face was associated with a higher probability of being rewarded. This work replicated previous findings from research in healthy individuals and patients with schizophrenia without pharmacological manipulation or after taking a placebo (Averbeck and Duchaine, 2009; Evans et al., 2011a; Evans et al., 2010; Furl et al., 2012). Additionally, the evidence showed that this bias was attenuated by the administration of ropinirole and amisulpride in healthy controls (Chapter 3, page 73) and oxytocin in patients with schizophrenia (Chapter 6, page 218) so that, after the administration of these drugs, participants no longer demonstrate a preference, or bias, for choosing either the happy or angry face.

In healthy controls (Chapter 3) the attenuation of bias when deciding between two emotionally valenced faces after ropinirole administration was associated with an

increase in neural activity within the dACC and dmPFC, areas that are well-known to be involved in decision-making (Botvinick, 2007), social processing (Phan et al., 2002a) and where D_2 dopaminergic binding occurs (Ko et al., 2009; Lumme et al., 2006). However, after amisulpride administration no significant changes in neural activity were observed when deciding between two emotionally valenced faces. These changes in neural activation patterns in response to dopaminergic manipulation that were present in healthy controls were absent in patients with schizophrenia when deciding between two emotionally valenced faces (Chapter 4). However, when compared to healthy controls who had received a placebo, patients with schizophrenia demonstrated attenuation of neural activity in the thalamus, primarily within the MDN, a region repeatedly shown to be abnormal in patients with schizophrenia, both structurally and functionally (Andrews et al., 2006; Byne et al., 2001; Mitelman et al., 2005; Pakkenberg, 1990). Furthermore, when looking at decision-making in general (i.e. across emotionally-valenced and neutral blocks), patients with schizophrenia show decreased neural activity in a wider network of brain regions including the thalamus, cerebellum and mPFC. In patients with schizophrenia, deficits within this network have previously been shown by others using both MRI and positron emission tomography (PET) and have been posited to demonstrate "cognitive dysmetria" or poor mental coordination (Andreasen, 1997; Andreasen et al., 1996; Andreasen et al., 1998) possibly indicative of dysconnectivity within these regions (Friston, 2005; Stephan et al., 2006; Stephan et al., 2009).

As predicted, directionally concordant effects were found between healthy controls who had taken amisulpride and patients with schizophrenia. Both groups exhibited attenuated neural activity within the cerebellum extending through the tentorium into

the fusiform gyrus - regions associated with social and facial processing (Anilkumar et al., 2008; Grill-Spector et al., 2004; Haxby et al., 2000; Van Overwalle et al., 2014) - when deciding between two neutral faces, compared to healthy controls who had taken a placebo. This suggests during facial identification, as opposed to emotional identification, both patients with schizophrenia and healthy controls who have taken amisulpride appear to recruit these regions associated with social and facial processing less despite performing the task at a similar level as the other groups. However, further analysis will need to be done to determine how these changes affected decision-making without altering performance.

After being administered oxytocin (Chapter 6), attenuation of bias toward the happy face is accompanied by attenuation of neural activity in regions associated with social processing, such as the amygdala and TPJ, during decision-making involving emotionally valenced stimuli. This finding corresponded to the observations from Chapter 3, which showed that attenuation of bias during decision-making between two emotionally valenced faces after ropinirole administration was also accompanied by an attenuation of neural activity within the amygdala. The amygdala is viewed as a cardinal area for emotional processing (Costafreda et al., 2008; Pessoa and Adolphs, 2010; Sergerie et al., 2008), and is part of the mesolimbic dopamine pathway (Koob and Swerdlow, 1988), suggesting a possible overlap between dopaminergic and oxytocinergic activity (Abi-Dargham, 2012; Rosenfeld et al., 2011). Attenuation of neural activity in the amygdala and TPJ may reflect that oxytocin may attenuate the aversion toward choosing the angry, in addition to decreasing the affinity toward choosing the happy face.

In addition to these main findings, exploratory analyses revealed further interesting findings. For example, in Chapter 4 it was found that patients with schizophrenia demonstrated greater neural activity correlating with RPE in the ventral striatum than healthy controls who had taken placebo. In most other studies exploring RPE in patients with schizophrenia the opposite pattern has been observed where patients with schizophrenia generally show less neural activity for RPE than healthy controls. The current finding may be attributable to the simplicity of the current model in comparison to the models, such as Q learning (Gradin et al., 2011; Murray et al., 2008). It is also possible that the patients in our study were more sensitive to reward feedback than the healthy controls or that they recruited more compensatory networks for processing reward than healthy controls within the striatum to be able to perform the task at a similar level as the healthy controls. Furthermore, the other studies outlined in this thesis looking at RPE, used greater monetary rewards than our study and one study even showed that, in addition to the modulatory effect of dopamine agonists and antagonists, in healthy participants, the degree of monetary reward also had a modulatory effect on neural activity such that higher monetary rewards were associated with higher neural activity (Pleger et al., 2009). When looking at the effects of dopamine on decision-making in trials investigating loss aversion or when deciding between two options associated with low reward probability, no effects of dopaminergic manipulation were seen (Jocham et al., 2011; Pessiglione et al., 2006), suggesting that the effects from these other papers may be specific to higher monetary reward. One way to assess this further would be to implement similar models as used in previous papers and compare the results in neural activity from these models and the model presented here.

Additionally, in Chapter 6, correlation measures were assessed when looking at neural activity correlating with RPE in the ventral striatum after oxytocin administration in patients with schizophrenia in the emotionally valenced face condition. The results showed strong (positive) correlations between positive and total illness symptoms with neural activity after oxytocin administration in patients with schizophrenia. Furthermore, when assessing correlations between symptom scores and the difference in neural activity in the ventral striatum between oxytocin and placebo administration, a positive correlation was also found between positive symptoms, but not total symptoms, and neural activity for RPE. This indicates that patients with schizophrenia who exhibit higher positive symptoms, despite being stable on their medication, appear to show the greatest changes in neural activity after oxytocin administration and suggests that, for these patients, oxytocin administration may be of particular clinical benefit.

Previously it was also shown that bias toward choosing a happy face is attenuated in healthy controls through the administration of oxytocin (Evans et al., 2010). Chapter 3 of this thesis shows that in healthy controls ropinirole and amisulpride also attenuate this bias such that neither face is favoured during decision-making. Furthermore, Chapter 6 demonstrates that oxytocin also attenuates this bias toward the happy face in patients with schizophrenia. Additionally, in healthy participants who received ropinirole and patients with schizophrenia who took oxytocin, attenuation of bias toward the happy face when deciding between two emotionally valenced faces was accompanied by an attenuation of neural activity within the amygdala. This finding is in line with studies showing that implicit processing of social stimuli after oxytocin administration was associated with attenuation of neural activity in the amygdala

(Domes et al., 2007b; Kirsch et al., 2005; Petrovic et al., 2008; Riem et al., 2011). As the amygdala has been suggested to be involved in the evaluation of biological significance (Pessoa and Adolphs, 2010) in terms of assigning personal or social value, and emotional arousal (McGaugh, 2005), attenuation of this region may signify that subjects are evaluating the faces more objectively without being as influenced by the emotional expressions. This is especially of clinical significance for patients with schizophrenia, as the attribution of aberrant salience to emotional faces could lead to patients believing that socially innocuous stimuli hold a more personal relevance to them. This process has specifically been suggested to underlie the formation and maintenance of paranoid delusions. This study shows that oxytocin and dopamine agonists attenuate neural activity relating to evaluation of emotional stimuli, as well as attenuating social bias without having a detrimental effect on task performance (i.e. choosing the face more associated with the higher probability of reward in lieu of the more biologically rewarding face). This implies that both ropinirole and oxytocin are capable of attenuating the attribution of biological significance to social stimuli that hold no personal relevance to the individuals viewing them; thus allowing for more objective and correct discrimination and classification of stimuli.

In general, the lack of overlap between differences in neural activity after dopaminergic perturbation and differences in neural activity between healthy controls and patients with schizophrenia is interesting because it shows that differences in neural activity within patients with schizophrenia cannot necessarily be explained by changes in dopamine alone. This is in line with contemporary ideas on the role of glutamate in schizophrenia (Coyle, 2006; Laruelle et al., 2003; Stone et al., 2007). However, these findings using dopaminergic manipulation and patients with

schizophrenia are complicated by many other factors which may have impacted on the findings. The first of these potential confounders is the presence of autoreceptors, or receptors which are capable of providing their own negative feedback without further neurochemical perturbation along the neuron. These act to control the synthesis and release of neurotransmitters, such as dopamine, mainly in the nigrostriatal and mesolimbic systems (Meltzer, 1980). The second complication arises from inherent issues with the dosing and standardisation of medication. Although dopaminergic perturbation was initially addressed as if consistent timing and dosage would produce similar effects across participants, this is known not to be the case. Dopaminergic perturbation is known to have a differential response across individuals. The variability for these effects is thought to occur across an inverted-U-shaped curve where both too much and too little dopamine can lead to impairments in cognition (Cools and D'Esposito, 2011). Furthermore, depending on the size of the participant, using the same dose could have a higher or lower impact on changes in dopamine binding within the brain. Those with higher BMI or body fat ratios will tend to absorb the drug differently than those with a lower fat content and BMI so that not all of the drug may make the journey to the brain to cross the blood brain barrier. Therefore, although the doses administered were in line with standard clinical doses, it is hard to say for all those involved in the study if the dosage used would have elicited enough of change in dopaminergic binding to prompt changes in neural activity.

This study was also limited by the fact that the concentration of dopamine was not standardised to each person. Fixed doses of dopamine agonists and antagonists were given to all individuals in the study and may have affected some more than others. Furthermore, dopamine levels within the bloodstream have also been shown to be

affected by fat content consumed throughout the day. Although care was taken to provide our subjects with qualitatively similar low-fat meals while they were at the Institute of Psychiatry for testing and instructions were given for appropriate meals on the testing day before their participation in the study, it was not possible to control what they had eaten before they attended the testing session. Therefore the peak dopamine concentrations may have differed between individuals. Plasma levels were not recorded, so it is impossible to tell how affected each individual was by the dopamine perturbation.

Furthermore, although changes in neural activity during dopaminergic perturbation are assumed to be driven by changes in dopaminergic binding, without directly measuring this binding it is impossible to be sure. However, changes in neural activity from both amisulpride and ropinirole corresponded with areas that previously showed reliable changes in dopaminergic binding after the administration of dopamine agonists (Ko et al., 2009; Lumme et al., 2006) and antipsychotics (Ito et al., 2009). Although both drugs show some affinity for other neurochemicals such as serotonin (Abbas et al., 2009; Dhir and Kulkarni, 2007), they both demonstrate a strong affinity for D_2 receptors (Alonso Cánovas et al., 2014; Green, 2002; Kaye and Nicholls, 2000). Thus, the effects observed in this study may also be due to each drug's effects over other neurochemicals, however, this is less likely for the reasons listed above.

Another possible confound is that all patients with schizophrenia, with the exception of two, were medicated. This makes it difficult to look at aberrant dopaminergic activity in an unbiased way. As all of our patients were clinically stable and antipsychotic efficacy has been found to correlate with D_2 receptor binding (Kapur and Remington, 2001), it is highly likely that most patients with schizophrenia were within

the optimal therapeutic window of 65-78% D_2 receptor blockade (Kapur and Remington, 2001). However, as this study was unable to ascertain specific binding measures within each participant, these numbers are purely speculative. Given that correlations were only found between changes in neural activity from amisulpride administration and patients with schizophrenia and none were found after ropinirole administration, it is probable these findings were due to similar dopaminergic receptor blockades. Furthermore, this study used mainly chronically ill patients with schizophrenia (average duration of illness 13.54 ± 8.76). It is therefore important to recognise that illness chronicity may have also affected the results. Given that most patients had been taking D_2 antagonist medication for most years of their illness, this may account for why neural activity in the patients with schizophrenia resembled healthy controls who had taken amisulpride.

In a similar vein, negative symptoms and cognitive deficits in schizophrenia are also thought to be brought about by decreases in dopamine D_1 receptors, which would not have been affected by the drugs that were administered in this study. However, given that the majority of the differences that we found between patients with schizophrenia and healthy controls were not in regions that are high in D_1 receptors, this is unlikely to be a substantial contributor to our results. More likely is the assertion that schizophrenia may be driven by other neurochemicals in addition to dopamine. An emerging theory is that schizophrenia is caused by aberrant glutamatergic levels (Coyle, 2006; Stephan et al., 2009; Stone et al., 2007). Although this may initially seem to conflict with the dopaminergic hypothesis of schizophrenia, it is possible that abnormalities in these neurotransmitter systems are interdependent (Laruelle et al., 2003; Stone et al., 2007). Glutamate acts on *N*-methyl-d-asparate (NMDA) receptors,

which may have a downstream or potentially upstream effect on dopaminergic transmission. To this effect, studies have shown that while some glutamate projection neurons into the hippocampus and cortex are modulated by dopamine (David et al., 2005; Hatzipetros and Yamamoto, 2006; Stone et al., 2007) some dopaminergic projections are also regulated by glutamate (Del Arco and Mora, 2008; Smith et al., 1998; Surmeier et al., 2007). Ketamine, a glutamate antagonist**,** has also been found to reduce D_2 receptor availability (Breier et al., 1998; Vollenweider et al., 2000), although the evidence with respect to this mechanism is not consistent (Aalto et al., 2002; Laruelle et al., 2003). Furthermore, one study has also shown that long-term administration of NMDA antagonists, acting on glutamate, disrupts dopaminergic transmission in a manner consistent with the deficits posited by the dopaminergic hypothesis of schizophrenia (Jentsch and Roth, 1999). Thus, while an initial aberrance in glutamate may give rise to schizophrenia, it appears symptoms associated with schizophrenia may still be driven by changes in dopamine.

Interestingly, numerous studies have shown glutamatergic abnormalities in schizophrenia within the thalamus (for a review see (Watis et al., 2008)). Elevated levels of glutamate in this region have been shown in both untreated first episode patients with schizophrenia and patients with chronic schizophrenia (Théberge et al., 2003; Théberge et al., 2002). Furthermore, an increase in glutamate in the thalamus was also found to positively correlate with the duration of illness (Théberge et al., 2003). Given the illness chronicity of the patients with schizophrenia involved in this study and the lack of findings in the thalamus after dopaminergic perturbation, it can be speculated that the significant differences observed in neural activity between the

healthy controls and patients with schizophrenia within the thalamus were driven by these differences in glutamate.

This thesis highlights the need for future research focussing on investigating neurochemical manipulations in schizophrenia to elucidate the neuropathology of this disorder. Current research strongly supports the role of dopamine in the instantiation and perseveration of symptomatology in schizophrenia, at least with regard to positive symptoms. However, it is also apparent that aberrant dopamine is not the only driving factor behind schizophrenia. In the future, it may be more conclusive to repeat this same task while using positron emission tomography (PET) in order to look at striatal D_2 binding during the task to see how healthy controls compare with patients with schizophrenia. It may also be of use to use first-episode unmedicated patients in order to be able to investigate dopaminergic binding differences without the potentially confounding effects of (prolonged) medication. Also of interest would be to include a comparison of glutamatergic manipulation to see if any variance in neural activity could be accounted for by changes in glutamate levels. Using the data acquired, it may be useful to do further analyses looking at connectivity measures within the patients with schizophrenia compared to the healthy controls to further explore the potential contributions of "cognitive dysmetria" between the thalamus, cerebellum and mPFC and to see if measures of dysconnectivity contribute to differences in neural activity between these groups. As for future directions in research using oxytocin, it would be of interest to see if the findings presented in this thesis also translate to female subjects and to see if there are any gender specific effects of oxytocin in female patients with schizophrenia. It would also be useful to include a healthy control arm to

see if they respond to oxytocin in the same way as patients with schizophrenia during this task.

I am currently preparing to do a network analysis of the data presented here using dynamic causal modelling to look at the effects of drug perturbation, as well as group effects on neural activation patterns. I am also preparing to use a more sophisticated behavioural model incorporating similar parameters to those explored in the papers explored in this thesis, particularly Q-learning, to further explore RPE differences between the patients with schizophrenia and healthy controls.

In conclusion, although this thesis did not find clear associations between dopaminergic manipulation in healthy controls and patients with schizophrenia, some attenuation in neural activity within the patients with schizophrenia was similar to healthy controls who had taken amisulpride. This suggests that, due to medication effects, the group of patients used in this study more closely resembled healthy controls who had taken amisulpride. However, the extensive differences in neural activity between the healthy controls and patients with schizophrenia cannot be accounted for by differences in dopaminergic activity alone. These findings support the notion that schizophrenia arises from the perturbation of further neurochemicals such as glutamate (Coyle, 2006) and may also involve aberrant communication between areas of high integration such as the thalamus and cerebellum (Andreasen et al., 1999).

Additionally, these findings support the notion that oxytocin administration in patients with schizophrenia may facilitate prosocial interactions by attenuating neural activity in regions which in patients with schizophrenia may be normally hyperactive due to attributing elevated biological significance to certain social and non-social stimuli. Thus

attenuation of neural activity in these regions may allow patients with schizophrenia to more objectively assess social and non-social stimuli.

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